Motion, Attention, and Visual Awareness

Correlation and Interference Studies of Human Visual Cognition

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For Leif and Joscha

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CHAPTER 1

Introduction

The Introduction will cover some major theoretical issues that are touched upon in the studies described in this thesis. The guiding challenge of our work was to investigate the relationship between conscious visual perception and brain activity, or more specifically the relationship between conscious motion perception and its underlying neural substrates. This is the search for what has been called the "neural correlates of consciousness". For a long time, neuroscientists have eschewed the study of consciousness or related topics, but in the last two decades, there has been renewed interest in the neural mechanisms underlying our subjective experience. An important problem for the investigation of consciousness is the relationship between attention and awareness. Since we often rely on subjects' reports to gain access to their inner states – in humans or other animals –, it is argued that there can be no consciousness without attention to the relevant stimulus. Only with attention subjects are able to report their experience and only then they are fully conscious of their mental processes. Others would argue that attention and consciousness are separable processes. They might be highly intertwined but, importantly, there are different candidate neural mechanisms that can be mapped onto the two concepts. The last issue discussed in the Introduction is concerned more with the methodological aspects of our studies, especially the combination of multiple methods in cognitive neuroscience. Method development is often the focus of investigation in the field of neuroscience because in many cases major scientific discoveries are only possible with the development of new tools. In our studies, in which we combined fMRI, TMS, and psychophysics methodology, we hope to show how method development can be profitably integrated with relevant empirical questions to gain new insights into human brain function.

Neural Correlates of Consciousness

The study of consciousness has recently been revived as a legitimate pursuit for empirical scientists. For a long time, consciousness had been considered an elusive phenomenon, only to be addressed in the context of speculative philosophy. One important driving force for the renewed interest in consciousness were the publications by Francis Crick and Christof Koch, starting in the early 90's, in which they devised an empirical research program specifically for the study of visual consciousness, which they considered most tractable at that time (Crick & Koch, 1990; Crick & Koch, 1995; Crick & Koch, 1998; Rees, Kreiman, & Koch, 2002; Crick & Koch, 2003; Koch, 2004). In their programmatic approach, they advised scientists to abandon the futile philosophical discussion and conceive of experiments addressing the question of how the technicolor richness of our visual experience could possibly be implemented in our brains. This together with the advent of modern techniques of functional brain mapping (fMRI, PET, TMS) as tools for the non-invasive investigation of brain activity in humans has lead to a large increase in the number of studies in cognitive neuroscience devoted to the problem of consciousness (Rees et al., 2002).

The collaborative work described in this thesis was inspired by the question of how awareness of a specific type of visual experience – motion perception – is implemented in the human brain. There are several more particular issues connected to this fundamental question. The most straightforward problem is one of localization: What are the brain areas that are selectively involved in the representation of visual content we are aware of. Although some authors would argue that straightforward localization is an implausible model of brain function (Singer, 1998; Tononi & Edelman, 1998), there has been considerable controversy about which areas are necessary and sufficient for visual awareness (Crick & Koch, 1995; Kleinschmidt,

Büchel, Zeki, & Frackowiak, 1998; Lumer, Friston, & Rees, 1998; Lumer & Rees, 1999; Beck, Rees, Frith, & Lavie, 2001; Pascual-Leone & Walsh, 2001; Tong, 2003). Especially the involvement of early visual areas down to primary visual cortex (V1) has been hotly debate in the field of cognitive neuroscience (Crick & Koch, 1995; Tong & Engel, 2001; Rees et al., 2002). Some authors claim that awareness only arises in frontoparietal networks associated with attentional and working-memory functions (Dehaene, Naccache, Cohen, Bihan, Mangin, Poline, & Rivière, 2001; Baars, 2002; Sergent, Baillet, & Dehaene, 2005). Other data support the idea that activity in V1 – possibly driven through feedback from higher areas – is necessary for visual awareness (Polonsky, Blake, Braun, & Heeger, 2000; Pascual-Leone & Walsh, 2001; Tong & Engel, 2001; Silvanto, Cowey, Lavie, & Walsh, 2005), including our fMRI study on apparent motion in Chapter 2. The second major subtopic is concerned with the dynamics of conscious processing. Although most cortical areas get activated in the first 100 ms after onset of an appropriate stimulus (Schmolesky, Wang, Hanes, Thompson, Leutgeb, Schall, & Leventhal, 1998), it is unlikely that generation of awareness is accomplished in the very first feedforward sweeps of processing; these early responses have often been associated with cortical reflexes or so called 'zombie' modes of processing that do not require conscious access (Goodale & Milner, 1992; Crick & Koch, 2003). It is more plausible that longer-lasting recurrent interactions between different areas are necessary for conscious processing, a view that is supported by data from EEG/MEG (Libet, Wright, Jr., Feinstein, & Pearl, 1979; Ahlfors, Simpson, Dale, Belliveau, Liu, Korvenoja, Virtanen, Huotilainen, Tootell, Aronen, & Ilmoniemi, 1999; Sergent et al., 2005) and TMS studies (Hotson, Braun, Herzberg, & Boman, 1994; Pascual-Leone & Walsh, 2001; Silvanto et al., 2005), but also from electrode recordings in macaques (Supèr, Spekreijse, & Lamme, 2001). Chapter 2 and 3 contain examples of studies where fMRI and TMS have been used to probe the recurrent nature and the timing of activity related to conscious motion perception. Another issue, related to the previous topic of timing, is one of neural coding in the conscious brain. It is clear that action potentials are fundamental for cortical processing; they are the necessary currency for propagation of activity through the cortical network. But an additional important aspect of neural activity is the exact relative timing of spiking activity from different neurons. It can be argued that timing is the most crucial aspect of neural processing because random spiking cannot propagate through multiple network stages due to the summing properties of dendrites: An action potential can only be produced when the input from several neurons is integrated and this process is highly timing-dependent. This implies that the activity of different neurons has to be coordinated in a very precise fashion to produce an output. It also implies that there is a substantial amount of dendritic processing that does not translate into axonal output. A prominent proposal for timing-dependent processing is the coding-by-synchrony hypothesis (Singer & Gray, 1995). It states that activity in different brain areas is coordinated in the millisecond range to allow distributed representation of stimulus features that belong to the same object. Depending on the underlying temporal resolution of the process it also allows a limited amount of multiplexing of different stimulus representations in interleaved neural assemblies. Additional types of temporal coding have been proposed (Rodriguez, George, Lachaux, Martinerie, Renault, & Varela, 1999; Varela, Lachaux, Rodriguez, & Martinerie, 2001; Huxter, Burgess, & O'Keefe, 2003; Dragoi & Buzsáki, 2006) but until now it is still unclear which role the different types of coding play for effective processing and representation in the brain (Shadlen & Movshon, 1999). The question of coding is especially prominent for perceptual representations because there seems to be a

principled gap between the third-person description of brain states and our conscious experience of those states. In comparison, such a puzzle does not arise on the motor side because it is clear that spikes are vital for muscle activity, although temporal coding might still play a major role in organizing spiking activity. The coding conundrum for conscious perception has been nicely captured in a small passage of Christof Koch's (2004) recent book on consciousness: "It is possible that the NCC [neural correlates of consciousness] are not expressed in the spiking activity of some neurons but, perhaps, in the concentration of free, intracellular calcium ions in the postsynaptic dendrites of their target cells. Or the invisible partners of neurons, *glia* cells that support, nurture and maintain nerve cells and their environment in the brain, might be directly involved (although this is unlikely)." This explanatory gap between distributed electrochemical activity in the brain and our first-person conscious experience might also be the reason why some outrageous proposals for neural correlates of consciousness, like quantum interactions between microtubules, are seriously discussed in the community (Penrose, 1989; for a nice critique, see Churchland & Grush, 1995). Since the techniques used in this work cannot capture neuronal activity directly with the necessary spatial and temporal resolution, our data cannot provide major insights into questions of coding in the brain. But the studies described in Chapters 2 and 4 seem to support the idea that neural processing is interactive in nature, highly distributed and flexible. Also, the human fMRI data from Chapter 2 are at variance with single-cell recordings of action potentials in macaques, suggesting that the BOLD signal captures neural processing that is associated with conscious perception but does not correspond to spiking activity.

What are the specific neural correlates of motion perception? The investigation of the cortical mechanisms of motion processing is an important field in cognitive neuroscience and one of the first descriptions of functional specialization has been made with respect to motion selectivity (Allman & Kaas, 1971; Dubner & Zeki, 1971). The prime candidates for the neural correlates of motion awareness are the middle temporal areas in macaques and humans (Zeki, 1974; Zeki, Watson, Lueck, Friston, Kennard, & Frackowiak, 1991; Tootell, Reppas, Kwong, Malach, Born, Brady, Rosen, & Belliveau, 1995; Goebel, Khorram-Sefat, Muckli, Hacker, & Singer, 1998). In lesion and stimulation studies in macaques and humans, it could be demonstrated that the MT areas are necessary for conscious perception of motion (Zihl, von Cramon, & Mai, 1983; Newsome & Paré, 1988; Salzman, Britten, & Newsome, 1990; Baker, Hess, & Zihl, 1991; Zihl, von Cramon, Mai, & Schmid, 1991; Beckers & Hömberg, 1992; Salzman, Murasugi, Britten, & Newsome, 1992; Hotson et al., 1994; Beckers & Zeki, 1995) and a direct relationship between activity in hMT/V5+ and motion perception has been demonstrated in several studies using bistable apparent motion (Muckli, Kriegeskorte, Lanfermann, Zanella, Singer, & Goebel, 2002; Sterzer, Russ, Preibisch, & Kleinschmidt, 2002) and the motion aftereffect (Tootell, Reppas, Dale, Look, Sereno, Malach, Brady, & Rosen, 1995; Culham, Dukelow, Vilis, Hassard, Gati, Menon, & Goodale, 1999; Théoret, Kobayashi, Ganis, Di Capua, & Pascual-Leone, 2002; but see Huk, Ress, & Heeger, 2001). But hMT/V5+ is not the only area that shows motion selectivity. Other important regions described in the literature are V3A (Tootell, Mendola, Hadjikhani, Ledden, Liu, Reppas, Sereno, & Dale, 1997; Moutoussis, Keliris, Kourtzi, & Logothetis, 2005), KO (Orban, Dupont, De Bruyn, Vogels, Vandenberghe, & Mortelmans, 1995; Van Oostende, Sunaert, Van Hecke, Marchal, & Orban, 1997; Dupont, De Bruyn, Vandenberghe, Rosier, Michiels, Marchal, Mortelmans, & Orban, 1997), different parietal areas (Sunaert, Van Hecke, Marchal, & Orban, 1999; Claeys, Lindsey, De Schutter, & Orban, 2003; Williams, Elfar, Eskandar, Toth, & Assad, 2003), and even areas in the anterior temporal

cortex (Zhuo, Zhou, Rao, Wang, Meng, Chen, Zhou, & Chen, 2003). In addition, it has been proposed that recurrent interactions between hMT/V5+ and V1 are necessary for phenomenal awareness of motion (Pascual-Leone & Walsh, 2001; Silvanto et al., 2005). This model is also supported by our work: Activity in hMT/V5+ is necessary for processing the motion aspect of a stimulus (Chapter 3), but feedback interactions with V1 play a significant role in the complete representation of moving objects (Chapter 2).

Attention and Awareness

In one of his classic papers, the philosopher Ned Block (Block, 1995) suggested a basic distinction between two types of consciousness: phenomenal and access consciousness. 'Phenomenal consciousness' refers to the qualitative nature of our subjective experience, i.e., the different ways in which we sense the world with different modalities. 'Access consciousness' is concerned with our ability to explicitly grasp certain kinds of information and use them in further cognitive processing (for thought processes, logical inferences, or speech production). In psychological terms, these concepts can be mapped onto the dimensions of conscious perception and attention, respectively. A recent debate in philosophy and cognitive neuroscience has revolved around the question whether conscious perception and attention are separable processes or necessarily conflated. Apart from Block's conceptual analysis, there were several results from psychophysical and neuroimaging studies stimulating the discussion. In the 'Inattentional Blindness' and 'Change Blindness' paradigms, observers fail to report new stimuli or major changes in stimulation, although they are attending the respective displays (Mack & Rock, 1998; Simons & Chabris, 1999; Simons, Franconeri, & Reimer, 2000). These results have been taken as evidence for the dependence of conscious perception on attention. Observers do not perceive the stimuli or changes just because they do not attend the right locus in the stimulus arrays (but see Simons & Rensink, 2005). An fMRI study of change blindness found that detected stimulus changes in contrast to undetected changes produced activity in a frontoparietal network previously associated with attentional processes (Beck et al., 2001). Also other studies, using bistable paradigms, such as binocular rivalry and multistable figures, found similar frontoparietal activations due to changes of conscious perception (Kleinschmidt et al., 1998; Lumer et al., 1998; Lumer & Rees, 1999).

Although the methodology of the above experiments can be considered valid and their results have been replicated in several studies, the interpretation of the data has not been without criticism. A major problem with the interpretation is that in all the experiments the definition of conscious states was dependent on the observers' reports. Subjective report is taken as the gold standard for consciousness because it is the most direct way of knowing about conscious perception, but it has to be taken into account that multiple processes can be involved in what is considered direct access to subjective experience. Most importantly, it is begging the question against any differentiation of phenomenal consciousness and attention if only reported or detected perceptual contents are considered conscious. A different theoretical picture can be sketched if one takes the differentiation between phenomenal and access consciousness seriously. The alternative scheme is supported by philosophical as well as empirical studies. First of all, other studies investigating binocular rivalry also found activity modulations corresponding to observers' conscious experience in the early visual cortex (Polonsky et al., 2000; Tong & Engel, 2001; Lee, Blake, & Heeger, 2005) even down to the lateral geniculate nucleus (LGN) of the thalamus (Haynes, Deichmann, & Rees, 2005; Wunderlich, Schneider, & Kastner, 2005). This implies

that V1 and maybe even the LGN might be involved in the representation of our subjective experience. It has been suggested that these activity modulations in early visual areas corresponding to our visual awareness are not produced by feedforward propagation of activity but through recurrent interactions between regions (Lamme & Roelfsema, 2000; Lamme, Zipser, & Spekreijse, 2002; Lamme, 2003; Block, 2005). Lamme (2003) has argued that specifically feedback activation of early areas by higher areas would be a good candidate for the neural correlate of phenomenal consciousness. These phenomenal contents can be picked up by attentional mechanisms for further processing only when the recurrent activity in modality-specific areas is integrated with processing in fronto-parietal networks. On this account, there is a clear distinction between phenomenal consciousness and attention in neural as well as conceptual terms. Our studies in Chapter 5 and 6 support the idea that phenomenal awareness and attention are interacting but distinct processes. We tested how strong bistable stimuli like apparent motion and binocular rivalry can be biased by observers' voluntary attention. The results showed that observers could easily control apparent motion but not binocular rivalry, suggesting that, depending on the paradigm, there are neural mechanisms associated with consciousness that are not amenable and not determined by attentional processes.

Multiple Methods – Multiple Insights

Methodological innovations have been a driving force in the development of the cognitive-neuroscience field. A major factor was the availability of PET scanners for research purposes and the development of functional MRI in the early 90's. Especially for fMRI, the growth in journal publications over the last decade has been exponential. The use of fMRI allowed to non-invasively visualize activity in the whole brain during different stimulus and task conditions. Although the potential of fMRI to gain insight into human brain function is high, the method also has its limitations. The approach is correlative in nature, i.e., it provides an indirect measure of neural activity that is associated with certain conditions, but it does not allow inferences on causality because the brain activity is never manipulated by the experimenter. Therefore, it would be ideal to have a supplementary tool to selectively manipulate activity in discrete brain regions. This tool is available for research in humans since more than two decades: transcranial magnetic stimulation (TMS) (Barker, Jalinous, & Freeston, 1985). With TMS, one can apply non-invasively a fast-switching magnetic field to the brain that induces electric currents. These currents can lead to depolarization and activation of neuronal elements. Depending on the exact stimulation parameters, TMS can have inhibitory or facilitative effects on processing in a given cortical region (Hallett, 2000; Pascual-Leone, Walsh, & Rothwell, 2000; Cowey & Walsh, 2001). TMS has been used most extensively in the motor system (Barker et al., 1985; Pascual-Leone, Grafman, & Hallett, 1994; Fadiga, Fogassi, Pavesi, & Rizzolatti, 1995; Muellbacher, Ziemann, Wissel, Dang, Kofler, Facchini, Boroojerdi, Poewe, & Hallett, 2002), but also for the investigation of visual perception (Amassian, Cracco, Maccabee, Cracco, Rudell, & Eberle, 1989; Beckers & Hömberg, 1991; Beckers & Hömberg, 1992; Amassian, Cracco, Maccabee, Cracco, Rudell, & Eberle, 1993; Amassian, Maccabee, Cracco, Cracco, Rudell, & Eberle, 1993; Pascual-Leone & Walsh, 2001) and more cognitive processes like imagery (Kosslyn, Pascual-Leone, Felician, Camposano, Keenan, Thompson, Ganis, Sukel, & Alpert, 1999; Sack, Sperling, Prvulovic, Formisano, Goebel, Di Salle, Dierks, & Linden, 2002; Sack, Camprodon, Pascual-Leone, & Goebel, 2005), visuospatial tasks (Hilgetag, Théoret, & Pascual-Leone, 2001; Sack, Hubl, Prvulovic, Formisano, Jandl, Zanella, Maurer, Goebel, Dierks, & Linden, 2002), or working memory (Beckers &

Hömberg, 1991; Rossi, Cappa, Babiloni, Pasqualetti, Miniussi, Carducci, Babiloni, & Rossini, 2001; Campana, Cowey, & Walsh, 2002; Mottaghy, Gangitano, Krause, & Pascual-Leone, 2003) among others. In addition to information about the functional relevance of an area for a given task, TMS can also provide insights into the dynamics of processing with millisecond resolution (Amassian et al., 1989; Hotson et al., 1994; Corthout, Hallett, & Cowey, 2003; Sack et al., 2005).

TMS and fMRI have their respective advantages when used in isolation but, in addition, there are different ways to combine the two techniques, which can provide further insights (Sack & Linden, 2003). The most straightforward way of combining the two is to use fMRI to identify functionally specialized brain areas in individual participants for later TMS application (Sack et al., 2002; Herwig, Abler, Schönfeldt-Lecuona, Wunderlich, Grothe, Spitzer, & Walter, 2003; Neggers, Langerak, Schutter, Mandl, Ramsey, Lemmens, & Postma, 2004). This way the heterogeneity of localization across individuals can be accommodated and also relatively small brain regions can be targeted reliably across several experimental sessions. We used this approach in our study described in Chapter 3, where we identified hMT/V5+ in preceding fMRI scans and then used TMS to probe the functional significance as well as the exact timing of motion processing in hMT/V5+. The complementary type of combination is also possible: fMRI following TMS application. In this case, long-term effects of magnetic stimulation can be measured as BOLD correlates. This combination only makes sense when the TMS-induced changes last for a longer time, so this option requires the utilization of repetitive TMS, where magnetic pulses are applied at a certain frequency during a longer interval, e.g., 1 Hz TMS for 10 min produces inhibitory effects at the respective cortical site. The last and most intricate way of combining the two methods is a simultaneous setup, TMS in the fMRI scanner. The first reports of simultaneous measurements came from only a few groups, but recently more labs have started to utilize the potential of directly visualizing the consequences of magnetic stimulation. Since TMS coils are made out of copper, they are entirely compatible with the scanner environment. Problems arise when the two magnetic fields interact during TMS pulses. This can be easily avoided if TMS is only applied during short scanning breaks between subsequent fMRI head-volume acquisitions. In that way, a high quality of the MRI signal can be assured. What remains is the interaction between the static scanner field (around 3 Tesla) and the highly dynamic magnetic field induced through the TMS coil (around 2 Tesla at maximum with gradients of up to 40 000 Tesla per second). This interaction leads to strong vibratory movements of the TMS coil and a much louder sound. These issues can be easily accommodated if the coil is fixed in the scanner and participants wear an appropriate noise protection. The data we report in Chapter 4 were acquired using a simultaneous setup. This is the first time the actual consequences of a so-called ‘virtual lesion’ during a cognitive task induced by TMS were studied directly. The study demonstrates how the TMS/fMRI combination provides not only new insights into the neural underpinnings of TMS effects but also offers a new picture of the networks involved in cognitive tasks.

References

Ahlfors, S.P., Simpson, G.V., Dale, A.M., Belliveau, J.W., Liu, A.K., Korvenoja, A., Virtanen, J., Huotilainen, M., Tootell, R.B.H., Aronen, H.J., & Ilmoniemi, R.J. (1999). Spatiotemporal activity of a cortical network for processing visual motion revealed by MEG and fMRI. *J. Neurophysiol., 82*, 2545-2555.

Allman, J.M., & Kaas, J.H. (1971). A representation of the visual field in the caudal third of the middle temporal gyrus of the owl monkey (Aotus trivirgatus). *Brain Res., 31*, 85-105.

Amassian, V.E., Cracco, R.Q., Maccabee, P.J., Cracco, J.B., Rudell, A., & Eberle, L. (1989). Suppression of visual perception by magnetic coil stimulation of human occipital cortex. *Electroencephalogr. Clin. Neurophysiol., 74*, 458-462.

Amassian, V.E., Cracco, R.Q., Maccabee, P.J., Cracco, J.B., Rudell, A.P., & Eberle, L. (1993). Unmasking human visual perception with the magnetic coil and its relationship to hemispheric asymmetry. *Brain Res., 605*, 312-316.

Amassian, V.E., Maccabee, P.J., Cracco, R.Q., Cracco, J.B., Rudell, A.P., & Eberle, L. (1993). Measurement of information processing delays in human visual cortex with repetitive magnetic coil stimulation. *Brain Res., 605*, 317-321.

Baars, B.J. (2002). The conscious access hypothesis: origins and recent evidence. *Trends Cogn. Sci., 6*, 47-52.

Baker, C.L., Hess, R.F., & Zihl, J. (1991). Residual motion perception in a "motion-blind" patient, assessed with limited-lifetime random dot stimuli. *J. Neurosci., 11*, 454-461.

Barker, A.T., Jalinous, R., & Freeston, I.L. (1985). Non-invasive magnetic stimulation of human motor cortex. *Lancet, 1*, 1106-1107.

Beck, D.M., Rees, G., Frith, C.D., & Lavie, N. (2001). Neural correlates of change detection and change blindness. *Nat. Neurosci., 4*, 645-650.

Beckers, G., & Hömberg, V. (1991). Impairment of visual perception and visual short term memory scanning by transcranial magnetic stimulation of occipital cortex. *Exp. Brain Res., 87*, 421-432.

Beckers, G., & Hömberg, V. (1992). Cerebral visual motion blindness: transitory akinetopsia induced by transcranial magnetic stimulation of human area V5. *Proc. R. Soc. Lond. B Biol. Sci., 249*, 173-178.

Beckers, G., & Zeki, S. (1995). The consequences of inactivating areas V1 and V5 on visual motion perception. *Brain, 118*, 49-60.

Block, N. (1995). On a confusion about a function of consciousness. *Behav. Brain Sci., 18*, 227-247.

Block, N. (2005). Two neural correlates of consciousness. *Trends Cogn. Sci., 9*, 46-52.

Campana, G., Cowey, A., & Walsh, V. (2002). Priming of motion direction and area V5/MT: a test of perceptual memory. *Cereb. Cortex, 12*, 663-669.

Churchland, P.S., & Grush, R. (1995). Gaps in Penrose's toiling. *J. Conscious. Stud., 2*, 10-29.

Claeys, K.G., Lindsey, D.T., De Schutter, E., & Orban, G.A. (2003). A higher order motion region in human inferior parietal lobule: evidence from fMRI. *Neuron, 40*, 631-642.

Corthout, E., Hallett, M., & Cowey, A. (2003). Interference with vision by TMS over the occipital pole: a fourth period. *Neuroreport, 14*, 651-655.

Cowey, A., & Walsh, V. (2001). Tickling the brain: studying visual sensation, perception and cognition by transcranial magnetic stimulation. *Prog. Brain Res., 134*, 411-425.
Crick, F., & Koch, C. (1990). Some reflections on visual awareness. *Cold Spring Harb. Symp. Quant. Biol., 55*, 953-962.
Crick, F., & Koch, C. (1995). Are we aware of neural activity in primary visual cortex? *Nature, 375*, 121-123.
Crick, F., & Koch, C. (1998). Consciousness and neuroscience. *Cereb. Cortex, 8*, 97-107.
Crick, F., & Koch, C. (2003). A framework for consciousness. *Nat. Neurosci., 6*, 119-126.
Culham, J.C., Dukelow, S.P., Vilis, T., Hassard, F.A., Gati, J.S., Menon, R.S., & Goodale, M.A. (1999). Recovery of fMRI activation in motion area MT following storage of the motion aftereffect. *J. Neurophysiol., 81*, 388-393.
Dehaene, S., Naccache, L., Cohen, L., Bihan, D.L., Mangin, J.F., Poline, J.B., & Rivière, D. (2001). Cerebral mechanisms of word masking and unconscious repetition priming. *Nat. Neurosci., 4*, 752-758.
Dragoi, G., & Buzsáki, G. (2006). Temporal encoding of place sequences by hippocampal cell assemblies. *Neuron, 50*, 145-157.
Dubner, R., & Zeki, S.M. (1971). Response properties and receptive fields of cells in an anatomically defined region of the superior temporal sulcus in the monkey. *Brain Res., 35*, 528-532.
Dupont, P., De Bruyn, B., Vandenberghe, R., Rosier, A.M., Michiels, J., Marchal, G., Mortelmans, L., & Orban, G.A. (1997). The kinetic occipital region in human visual cortex. *Cereb. Cortex, 7*, 283-292.
Fadiga, L., Fogassi, L., Pavesi, G., & Rizzolatti, G. (1995). Motor facilitation during action observation: a magnetic stimulation study. *J. Neurophysiol., 73*, 2608-2611.
Goebel, R., Khorram-Sefat, D., Muckli, L., Hacker, H., & Singer, W. (1998). The constructive nature of vision: direct evidence from functional magnetic resonance imaging studies of apparent motion and motion imagery. *Eur. J. Neurosci., 10*, 1563-1573.
Goodale, M.A., & Milner, A.D. (1992). Separate visual pathways for perception and action. *Trends Neurosci., 15*, 20-25.
Hallett, M. (2000). Transcranial magnetic stimulation and the human brain. *Nature, 406*, 147-150.
Haynes, J.-D., Deichmann, R., & Rees, G. (2005). Eye-specific effects of binocular rivalry in the human lateral geniculate nucleus. *Nature, 438*, 496-499.
Herwig, U., Abler, B., Schönfeldt-Lecuona, C., Wunderlich, A., Grothe, J., Spitzer, M., & Walter, H. (2003). Verbal storage in a premotor-parietal network: evidence from fMRI-guided magnetic stimulation. *NeuroImage, 20*, 1032-1041.
Hilgetag, C.C., Théoret, H., & Pascual-Leone, A. (2001). Enhanced visual spatial attention ipsilateral to rTMS-induced 'virtual lesions' of human parietal cortex. *Nat. Neurosci., 4*, 953-957.
Hotson, J.R., Braun, D., Herzberg, W., & Boman, D. (1994). Transcranial magnetic stimulation of extrastriate cortex degrades human motion direction discrimination. *Vision Res., 34*, 2115-2123.
Huk, A.C., Ress, D., & Heeger, D.J. (2001). Neuronal basis of the motion aftereffect reconsidered. *Neuron, 32*, 161-172.
Huxter, J., Burgess, N., & O'Keefe, J. (2003). Independent rate and temporal coding in hippocampal pyramidal cells. *Nature, 425*, 828-832.

Kleinschmidt, A., Büchel, C., Zeki, S., & Frackowiak, R.S.J. (1998). Human brain activity during spontaneously reversing perception of ambiguous figures. *Proc. R. Soc. Lond. B Biol. Sci., 265*, 2427-2433.

Koch, C. (2004). *The Quest for Consciousness: a Neuroscientific Approach*. Greenwood Village, CO: Roberts & Company.

Kosslyn, S.M., Pascual-Leone, A., Felician, O., Camposano, S., Keenan, J.P., Thompson, W.L., Ganis, G., Sukel, K.E., & Alpert, N.M. (1999). The role of area 17 in visual imagery: convergent evidence from PET and rTMS. *Science, 284*, 167-170.

Lamme, V.A., Zipser, K., & Spekreijse, H. (2002). Masking interrupts figure-ground signals in V1. *J Cogn Neurosci., 14*, 1044-1053.

Lamme, V.A.F. (2003). Why visual attention and awareness are different. *Trends Cogn. Sci., 7*, 12-18.

Lamme, V.A.F., & Roelfsema, P.R. (2000). The distinct modes of vision offered by feedforward and recurrent processing. *Trends Neurosci., 23*, 571-579.

Lee, S.H., Blake, R., & Heeger, D.J. (2005). Traveling waves of activity in primary visual cortex during binocular rivalry. *Nat. Neurosci., 8*, 22-23.

Libet, B., Wright, E.W., Jr., Feinstein, B., & Pearl, D.K. (1979). Subjective referral of the timing for a conscious sensory experience: a functional role for the somatosensory specific projection system in man. *Brain, 102*, 193-224.

Lumer, E.D., Friston, K.J., & Rees, G. (1998). Neural correlates of perceptual rivalry in the human brain. *Science, 280*, 1930-1934.

Lumer, E.D., & Rees, G. (1999). Covariation of activity in visual and prefrontal cortex associated with subjective visual perception. *Proc. Natl. Acad. Sci. U. S. A, 96*, 1669-1673.

Mack, A., & Rock, I. (1998). *Inattentional Blindness*. Cambridge,MA: MIT Press.

Mottaghy, F.M., Gangitano, M., Krause, B.J., & Pascual-Leone, A. (2003). Chronometry of parietal and prefrontal activations in verbal working memory revealed by transcranial magnetic stimulation. *NeuroImage, 18*, 565-575.

Moutoussis, K., Keliris, G., Kourtzi, Z., & Logothetis, N. (2005). A binocular rivalry study of motion perception in the human brain. *Vision Res., 45*, 2231-2243.

Muckli, L., Kriegeskorte, N., Lanfermann, H., Zanella, F.E., Singer, W., & Goebel, R. (2002). Apparent motion: event-related functional magnetic resonance imaging of perceptual switches and states. *J. Neurosci., 22*, RC219 (1-5).

Muellbacher, W., Ziemann, U., Wissel, J., Dang, N., Kofler, M., Facchini, S., Boroojerdi, B., Poewe, W., & Hallett, M. (2002). Early consolidation in human primary motor cortex. *Nature, 415*, 640-644.

Neggers, S.F.W., Langerak, T.R., Schutter, D.J.L.G., Mandl, R.C.W., Ramsey, N.F., Lemmens, P.J.J., & Postma, A. (2004). A stereotactic method for image-guided transcranial magnetic stimulation validated with fMRI and motor-evoked potentials. *NeuroImage, 21*, 1805-1817.

Newsome, W.T., & Paré, E.B. (1988). A selective impairment of motion perception following lesions of the middle temporal visual area (MT). *J. Neurosci., 8*, 2201-2211.

Orban, G.A., Dupont, P., De Bruyn, B., Vogels, R., Vandenberghe, R., & Mortelmans, L. (1995). A motion area in human visual cortex. *Proc. Natl. Acad. Sci. USA, 92*, 993-997.

Pascual-Leone, A., Grafman, J., & Hallett, M. (1994). Modulation of cortical motor output maps during development of implicit and explicit knowledge. *Science, 263*, 1287-1289.

Pascual-Leone, A., & Walsh, V. (2001). Fast backprojections from the motion to the primary visual area necessary for visual awareness. *Science, 292*, 510-512.
Pascual-Leone, A., Walsh, V., & Rothwell, J. (2000). Transcranial magnetic stimulation in cognitive neuroscience--virtual lesion, chronometry, and functional connectivity. *Curr. Opin. Neurobiol., 10*, 232-237.
Penrose, R. (1989). *The Emperor's New Mind: Concerning Computers, Minds, and the Laws of Physics*. Oxford: Oxford University Press.
Polonsky, A., Blake, R., Braun, J., & Heeger, D.J. (2000). Neuronal activity in human primary visual cortex correlates with perception during binocular rivalry. *Nat. Neurosci., 3*, 1153-1159.
Rees, G., Kreiman, G., & Koch, C. (2002). Neural correlates of consciousness in humans. *Nat. Rev. Neurosci., 3*, 261-270.
Rodriguez, E., George, N., Lachaux, J.P., Martinerie, J., Renault, B., & Varela, F.J. (1999). Perception's shadow: long-distance synchronization of human brain activity. *Nature, 397*, 430-433.
Rossi, S., Cappa, S.F., Babiloni, C., Pasqualetti, P., Miniussi, C., Carducci, F., Babiloni, F., & Rossini, P.M. (2001). Prefrontal cortex in long-term memory: an "interference" approach using magnetic stimulation. *Nat. Neurosci., 4*, 948-952.
Sack, A.T., Camprodon, J.A., Pascual-Leone, A., & Goebel, R. (2005). The dynamics of interhemispheric compensatory processes in mental imagery. *Science, 308*, 702-704.
Sack, A.T., Hubl, D., Prvulovic, D., Formisano, E., Jandl, M., Zanella, F.E., Maurer, K., Goebel, R., Dierks, T., & Linden, D.E.J. (2002). The experimental combination of rTMS and fMRI reveals the functional relevance of parietal cortex for visuospatial functions. *Brain Res. Cogn. Brain Res., 13*, 85-93.
Sack, A.T., & Linden, D.E.J. (2003). Combining transcranial magnetic stimulation and functional imaging in cognitive brain research: possibilities and limitations. *Brain Res. Brain Res. Rev., 43*, 41-56.
Sack, A.T., Sperling, J.M., Prvulovic, D., Formisano, E., Goebel, R., Di Salle, F., Dierks, T., & Linden, D.E.J. (2002). Tracking the mind's image in the brain II: transcranial magnetic stimulation reveals parietal asymmetry in visuospatial imagery. *Neuron, 35*, 195-204.
Salzman, C.D., Britten, K.H., & Newsome, W.T. (1990). Cortical microstimulation influences perceptual judgements of motion direction. *Nature, 346*, 174-177.
Salzman, C.D., Murasugi, C.M., Britten, K.H., & Newsome, W.T. (1992). Microstimulation in visual area MT: effects on direction discrimination performance. *J. Neurosci., 12*, 2331-2355.
Schmolesky, M.T., Wang, Y., Hanes, D.P., Thompson, K.G., Leutgeb, S., Schall, J.D., & Leventhal, A.G. (1998). Signal timing across the macaque visual system. *J. Neurophysiol., 79*, 3272-3278.
Sergent, C., Baillet, S., & Dehaene, S. (2005). Timing of the brain events underlying access to consciousness during the attentional blink. *Nat. Neurosci., 8*, 1391-1400.
Shadlen, M.N., & Movshon, J.A. (1999). Synchrony unbound: a critical evaluation of the temporal binding hypothesis. *Neuron, 24*, 67-25.
Silvanto, J., Cowey, A., Lavie, N., & Walsh, V. (2005). Striate cortex (V1) activity gates awareness of motion. *Nat. Neurosci., 8*, 143-144.
Simons, D.J., & Chabris, C.F. (1999). Gorillas in our midst: sustained inattentional blindness for dynamic events. *Perception, 28*, 1059-1074.
Simons, D.J., Franconeri, S.L., & Reimer, R.L. (2000). Change blindness in the absence of a visual disruption. *Perception, 29*, 1143-1154.

Simons, D.J., & Rensink, R.A. (2005). Change blindness: past, present, and future. *Trends Cogn Sci., 9*, 16-20.
Singer, W. (1998). Consciousness and the structure of neuronal representations. *Philos. Trans. R. Soc. Lond. B Biol. Sci., 353*, 1829-1840.
Singer, W., & Gray, C.M. (1995). Visual feature integration and the temporal correlation hypothesis. *Annu. Rev. Neurosci., 18*, 555-586.
Sterzer, P., Russ, M.O., Preibisch, C., & Kleinschmidt, A. (2002). Neural correlates of spontaneous direction reversals in ambiguous apparent visual motion. *NeuroImage, 15*, 908-916.
Sunaert, S., Van Hecke, P., Marchal, G., & Orban, G.A. (1999). Motion-responsive regions of the human brain. *Exp. Brain Res., 127*, 355-370.
Supèr, H., Spekreijse, H., & Lamme, V.A.F. (2001). Two distinct modes of sensory processing observed in monkey primary visual cortex (V1). *Nat. Neurosci., 4*, 304-310.
Théoret, H., Kobayashi, M., Ganis, G., Di Capua, P., & Pascual-Leone, A. (2002). Repetitive transcranial magnetic stimulation of human area MT/V5 disrupts perception and storage of the motion aftereffect. *Neuropsychologia, 40*, 2280-2287.
Tong, F. (2003). Primary visual cortex and visual awareness. *Nat. Rev. Neurosci., 4*, 219-229.
Tong, F., & Engel, S.A. (2001). Interocular rivalry revealed in the human cortical blind-spot representation. *Nature, 411*, 195-199.
Tononi, G., & Edelman, G.M. (1998). Consciousness and complexity. *Science, 282*, 1846-1851.
Tootell, R.B.H., Mendola, J.D., Hadjikhani, N.K., Ledden, P.J., Liu, A.K., Reppas, J.B., Sereno, M.I., & Dale, A.M. (1997). Functional analysis of V3A and related areas in human visual cortex. *J. Neurosci., 17*, 7060-7078.
Tootell, R.B.H., Reppas, J.B., Dale, A.M., Look, R.B., Sereno, M.I., Malach, R., Brady, T.J., & Rosen, B.R. (1995). Visual motion aftereffect in human cortical area MT revealed by functional magnetic resonance imaging. *Nature, 375*, 139-141.
Tootell, R.B.H., Reppas, J.B., Kwong, K.K., Malach, R., Born, R.T., Brady, T.J., Rosen, B.R., & Belliveau, J.W. (1995). Functional analysis of human MT and related visual cortical areas using magnetic resonance imaging. *J. Neurosci., 15*, 3215-3230.
Van Oostende, S., Sunaert, S., Van Hecke, P., Marchal, G., & Orban, G.A. (1997). The kinetic occipital (KO) region in man: an fMRI study. *Cereb. Cortex, 7*, 690-701.
Varela, F., Lachaux, J.P., Rodriguez, E., & Martinerie, J. (2001). The brainweb: phase synchronization and large-scale integration. *Nat. Rev. Neurosci., 2*, 229-239.
Williams, Z.M., Elfar, J.C., Eskandar, E.N., Toth, L.J., & Assad, J.A. (2003). Parietal activity and the perceived direction of ambiguous apparent motion. *Nat. Neurosci., 6*, 616-623.
Wunderlich, K., Schneider, K.A., & Kastner, S. (2005). Neural correlates of binocular rivalry in the human lateral geniculate nucleus. *Nat. Neurosci., 8*, 1595-1602.
Zeki, S., Watson, J.D.G., Lueck, C.J., Friston, K.J., Kennard, C., & Frackowiak, R.S.J. (1991). A direct demonstration of functional specialization in human visual cortex. *J. Neurosci., 11*, 641-649.
Zeki, S.M. (1974). Functional organization of a visual area in the posterior bank of the superior temporal sulcus of the rhesus monkey. *J. Physiol., 236*, 549-573.
Zhuo, Y., Zhou, T.G., Rao, H.Y., Wang, J.J., Meng, M., Chen, M., Zhou, C., & Chen, L. (2003). Contributions of the visual ventral pathway to long-range apparent motion. *Science, 299*, 417-420.

Zihl, J., von Cramon, D., & Mai, N. (1983). Selective disturbance of movement vision after bilateral brain damage. *Brain, 106*, 313-340.
Zihl, J., von Cramon, D., Mai, N., & Schmid, C. (1991). Disturbance of movement vision after bilateral posterior brain damage. Further evidence and follow up observations. *Brain, 114*, 2235-2252.

CHAPTER 2

Primary visual cortex activity along the apparent-motion trace reflects illusory perception

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Abstract

The illusion of apparent motion can be induced when visual stimuli are successively presented at different locations. It has been shown in previous studies that motion-sensitive regions in extrastriate cortex are relevant for the processing of apparent motion, but it is unclear whether primary visual cortex (V1) is also involved in the representation of the illusory motion path. We investigated in human subjects apparent-motion-related activity in patches of V1 representing locations along the path of illusory stimulus motion using functional magnetic resonance imaging (fMRI). Here we show that apparent motion caused a blood-oxygenation-level-dependent (BOLD) response along the V1 representations of the apparent-motion path, including regions that were not directly activated by the apparent-motion-inducing stimuli. This response was unaltered when participants had to perform an attention-demanding task that diverted their attention away from the stimulus. With a bistable motion quartet, we confirmed that the activity was related to the conscious perception of movement. Our data suggest that V1 is part of the network that represents the illusory path of apparent motion. The activation in V1 can either be explained by lateral interactions within V1 or by feedback mechanisms from higher visual areas, especially the motion-sensitive area hMT/V5+.

Introduction

Apparent motion can be perceived when two spatially segregated visual stimuli are presented in succession (Wertheimer, 1912). The illusion persists even when the stimuli are widely separated, a phenomenon called 'long-range apparent motion' (here we use the term 'apparent motion' to refer to long-range apparent motion) (Braddick, 1980). In order to respond to apparent motion, neurons have to integrate information over a large part of visual space, spanning at least the distance between the two inducing stimuli. Neurons in the middle temporal (MT) area of the macaque have pronounced directional selectivity and receptive-field sizes of up to 25° visual angle (Dubner & Zeki, 1971; Mikami, Newsome, & Wurtz, 1986b; Newsome, Mikami, & Wurtz, 1986; Albright, 1993), which makes them ideally suited for the integration of apparent-motion-inducing stimuli. Several studies have shown that MT and its human homologue, the human MT complex (hMT/V5+), respond to stimulus conditions that induce apparent motion (Mikami, 1991; Goebel, Khorram-Sefat, Muckli, Hacker, & Singer, 1998; Muckli, Kriegeskorte, Lanfermann, Zanella, Singer, & Goebel, 2002). In contrast, receptive field sizes in early visual areas and especially primary visual cortex (V1) are too small to account for long-range interactions between stimuli (Gattass, Gross, & Sandell, 1981; Smith, Singh, Williams, & Greenlee, 2001; Angelucci, Levitt, Walton, Hupé, Bullier, & Lund, 2002; Stettler, Das, Bennett, & Gilbert, 2002). The fact that one actually observes spatially resolved movement between the inducing stimuli in apparent motion suggests that there could be a filling-in process in early visual areas that is driven by feedback from extrastriate regions with bigger receptive-field sizes. Especially back-projections from hMT/V5+ have been shown to be relevant for perception of motion and apparent motion (Seghier, Dojat, Delon-Martin, Rubin, Warnking, Segebarth, & Bullier, 2000; Pascual-Leone & Walsh, 2001; Antal, Kincses, Nitsche, & Paulus, 2003; Silvanto, Cowey, Lavie, & Walsh, 2005). A psychophysical study of visual interference along the illusory path of apparent motion has indeed suggested feedback processes acting on the level of V1 as a possible mechanism (Yantis & Nakama, 1998). Liu et al. (2004) have used functional magnetic resonance imaging (fMRI) to test whether the perceptual 'filling-in' has an early or late cortical locus. Using a visual display comprising of two concentric rings Liu and colleagues found a late cortical locus (hMT/V5+ and lateral occipital complex) but no activity in the path of apparent motion in early visual areas.

We used a different visual display to test the same hypotheses and report here about V1 activity along the illusory motion path. In order to investigate the topographic pattern of apparent-motion-related activity in V1, we used functional magnetic resonance imaging in humans to map the retinotopic representation of apparent motion. We specifically looked for activity in subregions that were not directly activated by the apparent-motion-inducing stimuli. Our results show that there is activity in V1 sites representing the illusory motion path that cannot be explained by the local characteristics of the stimulus alone. The influence of attention was controlled with a demanding center task, where subjects had to detect numbers in a rapidly changing stream of letters and numbers. Using a bistable motion-quartet stimulus (Neuhaus, 1930; Ramachandran & Anstis, 1985), we confirmed that the activity in V1 changes as a function of the subjectively perceived motion trace. Considering the separation between the apparent-motion stimuli, we argue that this activity is most likely caused by feedback projections from extrastriate regions with bigger and direction-selective receptive fields.

Methods

Subjects

Eight subjects (six male) participated in the fMRI experiments; their mean age was 29.2 years (range, 22 to 34 years). All subjects had normal or corrected-to-normal (one subject) vision. The participants received information on MRI and a questionnaire to check for potential health risks and contraindications. Volunteers gave their informed consent after having been introduced to the procedure in accordance with the declaration of Helsinki. All subjects participated in retinotopic mapping. Five subjects participated in Experiment 1, five subjects in Experiment 2, and six subjects in Experiment 3. Three of the subjects that participated in Experiment 1 participated also in Experiment 2 and 3. Five subjects of Experiment 2 participated in Experiment 3.

Stimuli

Stimuli were generated with custom-made software based on the Microsoft DirectX™ library (StimulDX, Brain Innovation, Maastricht, The Netherlands, http://www.brainvoyager.com). The stimuli were back-projected onto a frosted screen with a liquid-crystal-display projector (Sony, VPL PX 20) and a custom-made lens. Subjects viewed the screen through a mirror. Mirror and projection screen were fixed onto the head coil. Seven different kinds of stimuli were used in the experiments (see Figure 1; stimulus 1C was used only in Experiment 2 and stimulus 1H only in Experiment 3). The *apparent-motion* stimulus (Figure 1A) consisted of two white blinking squares (size, 1.8° visual angle) presented in alternation on a dark screen to the right side of the fixation cross. The squares were presented at an eccentricity of 9.5° visual angle (distance between squares, 16.5°). Stimulus duration was 150 ms with an inter-stimulus interval of 67 ms, corresponding to a presentation frequency of 2.3 Hz. This specific frequency was chosen according to previous results showing that the perception of apparent motion is strongest in an envelope from 2 to 3 Hz (Finlay & von Grünau, 1987; Selmes, Fulham, Finlay, Chorlton, & Manning, 1997). A *real-motion* stimulus (Figure 1B) was generated by presenting a white square in harmonious oscillation (location on the path equals the sine of time) on the perceived path of the *apparent-motion* stimulus (size, 1.8° visual angle). The endpoints of the oscillation were directly adjacent to the position of the apparent-motion-inducing squares. The maximum eccentricity of the squares was 8.0° and the distance between the endpoints of the motion path 13.3° (average speed, 66.5°s^{-1}). Two static stimuli were used to map the locations where the *apparent-motion* squares were presented (*upper* and *lower* checkerboard, Figure 1D and 1F) and one static stimulus to map the center region of the *apparent-motion* path (*middle* checkerboard, Figure 1E). The *middle* stimulus was located halfway between the two squares of the *apparent-motion* stimulus at an eccentricity of 5.0° (size, 1.8°). The static stimuli were checkerboards consisting of a 4x4 matrix of alternating black and white squares. The checkerboards inverted their contrast every 100 ms, corresponding to a presentation frequency of 5 Hz. The size of the squares was 3.6° (*upper* and *lower*) and 1.8° (*middle*).

In Experiment 2 we used an additional control stimulus (Figure 1C) that was identical to the *apparent-motion* stimulus except that the two squares were presented in synchrony, resulting in a presentation frequency of 4.6 Hz. To control for attention effects, we also introduced a demanding center task (Chaudhuri, 1990). Subjects saw a stream of alphanumeric characters instead of the fixation cross and had to

press a button whenever they detected a numeric character (see Figure 1G). The presentation frequency of the characters was 2 Hz and targets appeared with a probability of 0.125.

In Experiment 3, we presented four blinking squares in a rectangular configuration in which the diagonally opposing dots blinked simultaneously (Figure 1H). We presented two dots at approximately the same positions in the right visual field as in previous studies (Experiment 1 and 2). Two further dots were presented in the left visual field and were therefore not processed by ipsilateral V1 (Tootell, Mendola, Hadjikhani, Liu, & Dale, 1998). We adjusted for each subject the vertical distance of the squares in order to make the stimulus bistable.

Procedure

Each of the conditions in Experiment 1 (five conditions) and 2 (six conditions) was presented for approximately 12.5 s (six volumes) in a block design, separated from the next block by a fixation period of the same length. A complete presentation cycle consisted of the following sequence of conditions (with intervening fixations): *middle*, *apparent motion*, *upper*, *real motion*, and *lower* (60 volumes) in Experiment 1 and *middle*, *apparent motion*, *upper*, *real motion*, *lower*, and *flicker* (72 volumes) in Experiment 2. In each following cycle, the presentation order of the conditions was reversed with respect to the preceding cycle, providing a control for serial-order effects. A complete scan comprised five cycles of experimental conditions plus an additional eight volumes of fixation at the beginning of the scan (308 volumes for Experiment 1 and 368 volumes for Experiment 2). In Experiment 1, two complete scans were acquired. Subjects were asked to fixate and be attentive during the scans. In Experiment 2, four scans were done with each subject. In two scans of Experiment 2, the subjects had to perform the attention task, while in the other two scans they only had to fixate the alphanumeric stream of the attention task. In the two runs of Experiment 3, we presented the bistable motion quartet five times for 125 seconds (60 volumes each). The five presentation periods were separated by 21 seconds (10 volumes) of fixation. During the motion-quartet trials, subjects had to indicate their current percept (vertical vs. horizontal motion) by continuously pressing one of two buttons with their right index and middle fingers. They were instructed to apply a strict criterion for changes of perception.

Imaging

fMRI scanning was performed on a 1.5 Tesla Siemens Magnetom Vision scanner (Siemens, Erlangen, Germany) at the University Clinic in Frankfurt am Main. A gradient-recalled echo-planar-imaging (EPI) sequence was used with the following parameters: 16 or 18 slices, oriented approximately in parallel to the AC-PC plane (AC, anterior commisure; PC, posterior commissure); TR, 2081 ms; TE, 60 ms; FA, 90°; FOV, 210 mm; in-plane resolution, 3.44 x 3.44 mm; slice thickness, 4 mm; gap thickness, 0.4 mm. In addition, a T1-weighted anatomical scan was acquired for all subjects using a Siemens fast low-angle-shot (FLASH) sequence (isotropic voxel size 1 mm^3).

Data Analysis

Data were analyzed using the BrainVoyager™ 4.9 software package (Brain Innovation, Maastricht, The Netherlands, http://www.brainvoyager.com). The first four volumes of each scan were discarded to preclude T1 saturation effects. Preprocessing of the functional data included the following steps: (i) three-dimensional motion correction using the Levenberg-Marquardt algorithm, (ii) linear-

trend removal and temporal high-pass filtering at 0.01 Hz, (iii) slice-scan-time correction with sinc interpolation.

The statistical analysis was performed with multiple linear regression. For every voxel, the time course was regressed on a set of dummy-coded predictors representing the experimental conditions. To account for the shape and delay of the hemodynamic response (Boynton, Engel, Glover, & Heeger, 1996), the predictor time courses (box-car functions) were convolved with a gamma-variate function.

With the data from Experiment 2, five ROIs were defined in individual subjects for a more detailed analysis of activation patterns in V1 and hMT/V5+. The three mapping conditions – *upper*, *middle*, and *lower* – and the *real-motion* condition were used to determine four ROIs in V1. We used conjunction analyses to effectively restrict the ROIs to parts of V1 with a specific functional profile. For example, to find regions responding specifically to the *lower* mapping, the activation produced by the *lower* stimulus had to be significantly higher than the response to the *middle* as well as the *upper* stimulus. For the *real-motion* ROI in V1, the *real-motion* condition was contrasted with the *upper* and *lower* condition. The threshold was set to a Bonferroni-corrected p value of 0.1. The hMT/V5+ ROI was defined by a balanced contrast between *real motion* and the three mapping conditions (*upper*, *middle*, and *lower*). For four subjects, p values were set to less than 0.2 (Bonferroni-corrected). Only in one subject a more liberal significance level of $p < 0.002$ (uncorrected) had to be used.

To ensure that the increases in event-related activity were not influenced by the preceding conditions, we inspected the event-related time-course averages (Figures 2 and S1), which are aligned to an average baseline of 0% signal change for the period of 4 s before stimulation onset. The activation patterns for the ROIs were visualized by plotting the percent signal change of the peak response (corresponding to the average of the three time points around 8 s, 10 s, and 12 s) for the different conditions. The measurements with and without center task were analyzed separately. Statistical significance was assessed across subjects to validate the reliability of the effects in our group of participants.

For Experiment 3, we mapped the cortical representation of our inducing stimuli by a GLM analysis in which we looked for higher activity during motion-quartet stimulation as compared to baseline (mapping of all stimulus locations). In addition, we identified regions with higher activation for perceived vertical motion compared to perceived horizontal motion and baseline (conjunction analysis). From these regions we extracted event-related time courses to visualize the activation changes due to the perceptual switches form horizontal to vertical motion. To avoid unspecific stimulus-onset effects, the first perceptual phase of each stimulation block was excluded from the analysis.

Retinotopic Mapping

Phase-encoded retinotopic mapping was assessed in each subject and included mapping of eccentricity and polar angle (Engel, Rumelhart, Wandell, Lee, Glover, Chichilnisky, & Shadlen, 1994; Sereno, Dale, Reppas, Kwong, Belliveau, Brady, Rosen, & Tootell, 1995; Goebel et al., 1998; Linden, Kallenbach, Heinecke, Singer, & Goebel, 1999). In the eccentricity-mapping experiment, black and white checkerboard patterns were presented in a ring-shaped configuration and were flickered at a rate of 4 Hz. The ring started with a radius of 1° and slowly expanded to a radius of 12° within 96 s. In the polar-angle mapping experiment, the checkerboard pattern consisted of a ray-shaped disk segment subtending 22.5° of polar angle. The ray started at the right horizontal meridian and slowly rotated clockwise for a full cycle

of 360° within 96 s. Each mapping experiment consisted of seven repetitions of a full expansion or ten repetitions of rotation, respectively, each cycle lasting for 64 s.

The analysis of the retinotopic-mapping experiment was conducted by the use of a cross-correlation analysis. We used the predicted hemodynamic signal time course for the first 1/8 of a stimulation cycle (corresponding to 45° visual angle in the polar mapping experiment) and shifted this reference function successively in time (time steps correspond to the recording time for one volume, TR) (Linden et al., 1999). Sites activated at particular eccentricities and polar angles were identified through selecting the lag value that resulted in the highest cross-correlation value for a particular voxel. The obtained lag values at particular voxels were encoded in pseudocolor on corresponding surface patches (triangles) of the reconstructed cortical sheet. Based on the polar-angle mapping experiment, the boundaries of retinotopic cortical areas V1, V2, V3, VP, V3A and V4v were estimated manually on the inflated cortical surface and colored in shades of light and dark gray.

Cortical-Surface Reconstruction

The recorded high-resolution T1-weighted 3D recordings were used for surface reconstruction of both cortical hemispheres of each subject (Kriegeskorte & Goebel, 2001). The white/gray-matter border was segmented with a region-growing method preceded by inhomogeneity correction of signal intensity across space. The borders of the two resulting segmented subvolumes were tessellated to produce a surface reconstruction of the left hemisphere. The resulting surface was used as the reference mesh for projecting functional data on inflated representations. A morphed surface always possesses a link to the folded reference mesh so that functional data can be shown at the correct location of folded as well as inflated representations. This link was also used to keep geometric distortions to a minimum during inflation and flattening through inclusion of a morphing force that keeps the distances between vertices and the area of each triangle of the morphed surface as close as possible to the respective values of the folded reference mesh.

Results

Experiment 1

We determined the extent and borders of early visual areas V1-V3 (Figure S1) in a retinotopic-mapping experiment (Goebel et al., 1998). In a second session, subjects were presented with five different stimulus conditions. The *apparent-motion* stimulus (Figure 1A) consisted of two white squares blinking in alternation, presented on a dark screen to the right side of a fixation cross. For mapping of the apparent-motion path, a *real-motion* stimulus was generated that consisted of a white square moving along the perceived trajectory of the *apparent-motion* stimulus (Figure 1B). The remaining three conditions consisted of contrast-inverting checkerboards presented at three different locations to map the cortical representation of the apparent-motion-inducing stimuli (*upper* and *lower* site, Figure 1D and 1F) and one location on the path of apparent motion (*middle*, Figure 1E).

To demonstrate specific effects of apparent motion, data were analyzed in Experiment 1 using two different approaches. First, we described the spatial distribution of apparent-motion-driven activity in V1 using simple activation maps (*apparent motion* > *baseline*) Second, in an explorative manner, we searched for regions of interest (ROIs) within these activity maps that were not at all activated by the inducing stimuli. It is clearly expected that at the beginning and at the end of the

motion streak, locations are also activated by the upper or lower blinking square. Therefore, activity patterns from the *apparent-motion* map (see above) could be influenced by the effects of the inducing stimuli. The second strategy provides proof of principle that there is activity within the streak that is not activated at all by the inducing squares.

Following the first strategy (green map in Figures 2 and S1), we found that the activity evoked during *apparent motion* spanned the region of V1 representing the

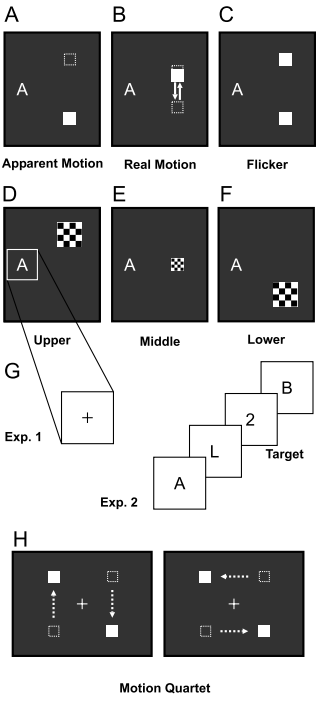

Figure 1. Stimuli used in Experiments 1 to 3. The apparent-motion (A) stimulus consisted of two white squares (size, 1.8°) blinking in alternation (2.3 Hz). The squares were presented at an eccentricity of 9.5° visual angle (distance between squares, 16.5°). The real-motion stimulus (B) consisted of a white square moving in harmonious oscillation (average speed, 66.5°s-1) on the perceived path of apparent motion. The endpoints of the movement were adjacent to the position of the apparent-motion squares (maximum eccentricity, 8.0°). The flicker control stimulus (C) from Experiment 2 was composed of two white squares (1.8°) that were blinking simultaneously at 4.6 Hz. For the mapping conditions, high-contrast inverting checkerboards were presented in the upper (D), middle (E), and lower (F) right visual field. Sizes were adjusted according to the cortical magnification factor in V1 to produce activated regions of a similar spatial extent (3.6° for the upper and lower stimuli presented at 9.5° eccentricity, 1.8° for the middle stimulus presented at 4.7° eccentricity). For the five conditions of Experiment 1 (A, B, D-F), subjects saw a white cross at the middle of the screen, which they had to fixate (G, upper part). In Experiment 2, a randomly generated stream of letters and digits was presented at 2 Hz in the middle of the screen (G, lower part). Subjects had to fixate the character stream and either passively view the stream or perform a digit-detection task. The motion quartet (H; Experiment 3) was composed of four white squares presented at eccentricities similar to the apparent-motion stimulus. Two squares from diagonally opposite corners were presented at the same time. The motion quartet can be seen in vertical (left part) or horizontal (right part) motion without any changes in the physical characteristics of the stimulus. Subjects had to fixate a white cross in the middle of the screen and had to report the perceived direction of movement (vertical or horizontal).

illusory motion path between the two apparent-motion-inducing stimuli ($t > 2$, $p < 0.05$ for each single-subject analysis). This streak of activity was always located on the *real-motion* path and, in four out of five subjects, was also activated by the *middle* mapping stimulus (Figure S1). Moreover, the activation maps for *real motion* and for *apparent motion* covered additional parts of V1 peripheral to the direct connection between the endpoints (Figure 2B and 2E). Following the second strategy, we found in four subjects ROIs within V1 between the mapped endpoints of the motion path that were activated in the *apparent-motion* condition but did not respond at all when the *upper* or *lower* mapping stimulus was presented alone (Figures 2 and S1).

Experiment 2

In the second experiment, we wanted to replicate our findings and control for possible alternative explanations for the apparent-motion-related activity. We added a task that required the subjects to divert their attention to the center of the visual field. We presented a stream of rapidly changing digits and letters instead of the fixation cross and instructed the subjects to respond to the appearance of the digits

(see Figure 1G). Separate MRI scans were acquired while the subjects either performed the attention task or passively viewed the character stream. At the same time, six different conditions were presented in the periphery: five conditions from Experiment 1 (*real motion*, *apparent motion*, *upper*, *middle*, and *lower*) and an additional control condition, in which two squares were blinking simultaneously at the *upper* and *lower* position (*flicker*, Figure 1C).

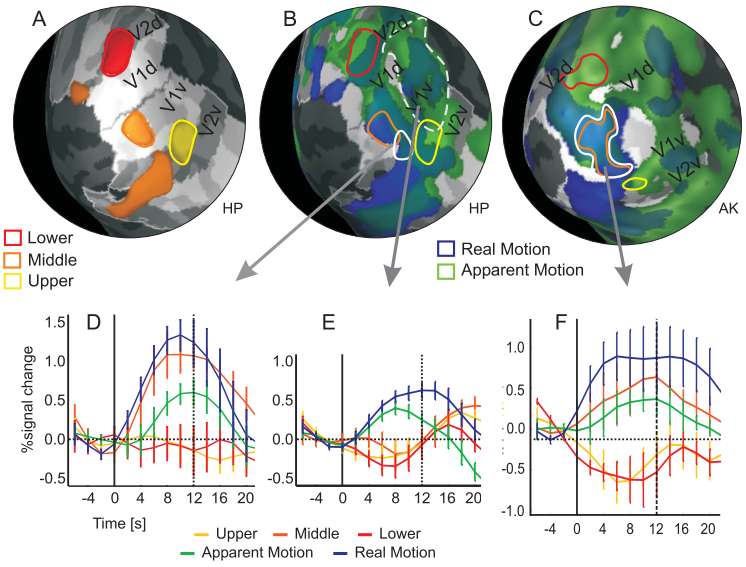

Figure 2. Activation pattern in primary visual cortex for Experiment 1. (A to C) Medio-posterior view on the inflated left occipital cortex of subject HP (A and B) and subject AK (C). All five subjects are shown in Figure S1. Gray-scale coloring of cortex indicates the extent of retinotopic visual areas (light gray: V1 and V3/VP; dark gray: V2, V4, and V3A) and the gyral pattern (concave surfaces are indicated in darker gray in the respective areas). (A) The cortical representations of the mapping stimuli are marked in color. The maps have been obtained by calculating a balanced contrast between the respective mapping condition of interest and the two other mapping conditions (e.g., middle vs. upper and lower). The thresholds of t-maps were individually adjusted to obtain patches of comparable size in V1: upper (yellow), $t(600) > 9.3$; middle (orange), $t(600) > 11.9$; and lower (red), $t(600) > 15.1$ (all $p << 0.001$). (B) Cortical activation maps for the apparent-motion (green) and real-motion (blue) condition compared to baseline (apparent motion in V1: $t(600) > 3.6$, $p < 0.0004$; real motion in V1: $t(600) > 18.6$, $p << 0.001$). Cortical representations of the mapping stimuli are indicated by colored outlines taken from (A). The white solid line indicates a patch of significant activation ($t(600) > 3$, $p < 0.003$) for the following conjunction of contrasts, which represents the ideal activation pattern: (middle > upper) & (middle > lower) & (apparent motion > upper) & (apparent motion > lower). The white dashed line marks a peripheral region in V1 with significant activation in response to apparent motion and real motion. (C) Same as (B) for subject AK. The white region with the optimal response pattern overlaps largely with the representation of the middle stimulus (in orange; see Figure S1 for details). (D) Event-related BOLD signal change for subject HP plotted over time from the patch outlined by the white solid line in (B) (solid black lines indicate stimulus onset, dotted lines stimulus offset). (E) Event-related BOLD signal change of the apparent-motion-activated (green) region from the eccentric parts of V1 outlined by the dashed white line in (B). This eccentric region responds to real motion and apparent motion but not to the middle stimulus. (F) Same as (D) for subject AK. Error bars correspond to standard errors of the mean.

As in Experiment 1, we first described the spatial distribution of apparent-motion-driven activity in V1 using contrast maps (*apparent motion* > *flicker*) and searched for ROIs within these activity maps that were not at all activated by the inducing stimuli. In addition to the two analysis strategies applied in Experiment 1, we used another two more objective approaches. As a third strategy, we selected ROIs in individual subjects from the representation of the apparent-motion path by use of the *middle* mapping condition (conjunction map: *middle* > *upper* AND *middle* > *lower*). In the

fourth approach, ROIs were selected by contrasting the *real-motion* condition with the outer mapping conditions. These ROI-based approaches are comparable to the one followed in the study of Liu et al. (2004).

Using strategy one and two, we replicated the previous findings (n = 5, three of which had already participated in Experiment 1). Again, we found apparent-motion-related activity between the endpoints (green map in Figures 3 and S2) in patches that were overlapping with regions activated by *real motion* (blue map) and the *middle* mapping stimulus. Moreover, the activation maps for *real motion* and for *apparent motion* covered additional parts of V1 peripheral to the direct connection between the endpoints. The ROI time courses show that activated regions in the middle of the motion streak responded exclusively to *middle* mapping, *real motion*, and *apparent motion* but not to *upper* or *lower* mapping stimulation. The activation of these not directly stimulated areas remained significant in seven out of ten single

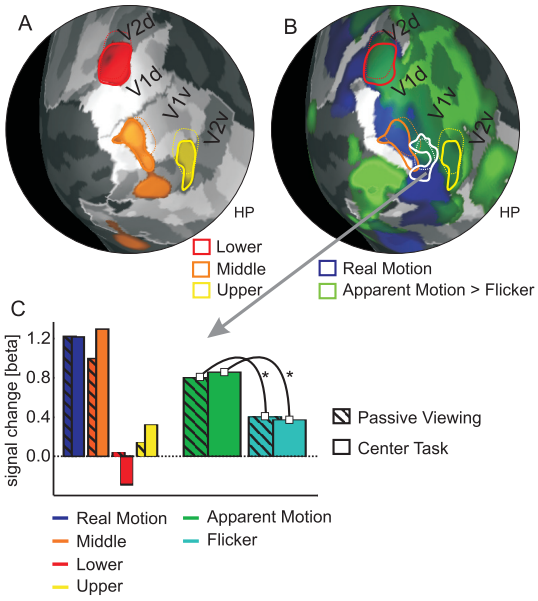

Figure 3. Cortical Activation in Primary Visual Cortex for Experiment 2. (A) Left occipital cortex of subject HP (all 5 subjects are shown in Figure S2) with superimposed contrast maps indicating the cortical representation of the stimulus positions: upper (yellow), t(1445) > 15; middle (orange), t(1445) > 12; and lower (red), t(1445) > 9.3 (all p << 0.001). For comparison, the patches from Experiment 1 (see Figure 1) are marked with dotted lines. (B) Cortical activation maps for apparent motion (green) and real motion (blue). In this case, apparent motion is contrasted with the flicker control condition (apparent motion > flicker in V1: t(1445) > 3.6, p < 0.0004); real motion is compared to fixation baseline (real motion > baseline in V1: t(1445) > 18.6, p << 0.001). The white line indicates an example of a significant (t > 2.2, p < 0.05) contrast conjunction: (middle > upper) & (middle > lower) & (apparent motion > flicker). (C) BOLD activity profile of the region indicated by the white line in (B). Bars indicate average activity during the respective conditions expressed in beta weights from a GLM analysis.

comparisons when we compared the apparent-motion-related activity to the activity caused by the *flicker* control condition (Figure S2). In this condition, the endpoints were stimulated in the same way as during apparent-motion induction, except that the squares were presented simultaneously and did not produce apparent motion (contrast *apparent motion* vs. *flicker*; $t(1445) > 2$, $p < 0.05$ in the significant single-subject analyses).

Following the strategy three and four, we computed event-related averages of V1 activity for different ROIs (Figure 4). The four ROIs were defined separately in individual subjects as parts of V1 that showed a significant response to one of the three mapping conditions (*upper*, *lower*, and *middle*) or to the *real-motion* condition.

The peak response relative to baseline was then compared for the different conditions and *t*-tests were computed across subjects. The ROIs for the *upper* and *lower* condition showed the expected response profile. Activation was strong for the respective mapping stimuli as well as for *flicker* and *apparent motion*, which were presented at the same location as the mapping conditions. The regions also showed a substantial response to *real motion*, probably due to larger receptive field sizes in the periphery and because the *real-motion* square overlapped with the outer mapping

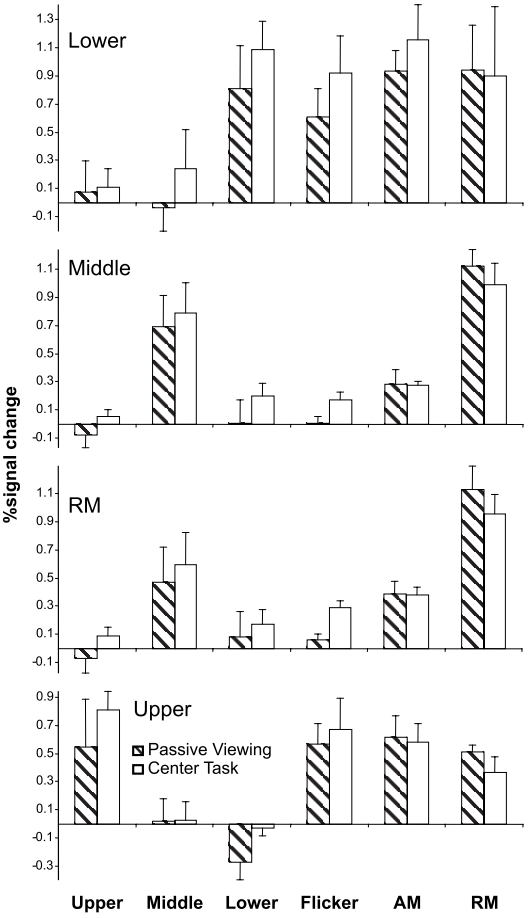

Figure 4. Response profile for different regions of interest in primary visual cortex for Experiment 2. The four panels correspond to four regions of interest (ROIs) that were defined in primary visual cortex by the respective conditions. To determine the ROIs for the three mapping conditions - *upper*, *middle*, and *lower* - the relevant condition was contrasted with the remaining two mapping conditions in a conjunction analysis (e.g., *upper* > *lower* & *upper* > *middle*). For the *real-motion* ROI, the *real-motion* condition was contrasted with the *upper* and *lower* mapping conditions (conjunction analysis). The bars designate percent signal change of the peak response relative to baseline for the different conditions (see Materials and Methods). The hatched bars are activations from runs with passive viewing only, and the unhatched bars are from runs with center task. For both the *real-motion* and *middle* ROI, the response to the *apparent-motion* stimulus is significantly larger than the response to the *flicker* squares. This is not the case for the *upper* and *lower* ROI. Error bars correspond to standard errors of the mean.

stimuli. There was no significant difference in the responses to the *apparent-motion* and *flicker* conditions ($p > 0.10$), suggesting that the two conditions were equivalent in terms of the local activity produced by the inducing stimuli. For the two ROIs on the path of apparent motion, *middle* mapping and *real motion*, the response profile looked different: For both regions, *real motion* produced the strongest activation, followed by the *middle* condition. In addition, there was a reliable response to *apparent motion* that was higher than the activity induced by the *flicker* squares. This effect decreased when the subjects' attention was focused on the letter-digits discrimination task (Figures 4 and S2) but was still significant ($p < 0.05$). Notably, the

decrease was not due to a reduction of apparent-motion-related activity but to an increased activity during the *flicker* control condition.

It has been demonstrated in previous fMRI studies that spatial attention strongly modulates activation in visual cortical areas down to primary visual cortex (Kastner, De Weerd, Desimone, & Ungerleider, 1998; Tootell, Hadjikhani, Hall, Marrett, Vanduffel, Vaughan, & Dale, 1998; Brefczynski & DeYoe, 1999; Gandhi, Heeger, & Boynton, 1999; Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999; Somers, Dale, Seiffert, & Tootell, 1999). To validate the effectiveness of our attention-demanding center task, we compared the activation in hMT/V5+ for the different conditions in runs with center task to the activation found with passive viewing (Figure 5). In addition, we looked at the attentional modulation in V1 at the *upper* and *lower* locations (Figure 4). In hMT/V5+, the general activation level was highest for *real motion* and *apparent motion* followed by *flicker* and the mapping stimuli (Figure 5). For both task conditions, passive viewing and center task, hMT/V5+ was activated significantly stronger for *apparent motion* than for *flicker* ($t(7247) > 2.7$, $p < 0.01$), in correspondence with the apparent-motion sensitivity of hMT/V5+ (Goebel et al., 1998; Muckli et al., 2002). We computed an attentional-modulation index (AMI) (Kastner et al., 1999) for the three main conditions of interest, *real motion*, *apparent motion*, and *flicker*. The AMI equals the difference between the responses of the passive viewing and center task runs normalized by the response of the passive viewing runs [(passive viewing - center task)/passive viewing]. A positive AMI value indicates a reduction in activation for the center task runs. In hMT/V5+ the AMI was 0.57 for *flicker*, 0.48 for *apparent motion*, and 0.41 for *real motion*. The very high AMI values show that the subjects' attention was efficiently diverted from the peripherally presented stimuli. In contrast to the results in hMT/V5+, the pattern of attentional modulation was very different in the V1 ROIs (Figure 4). Only *real motion* showed a positive AMI with 0.20 for the *lower* ROI and 0.34 for the *upper* ROI. The other relevant conditions showed an enhanced response with the center task; their AMI values ranged from -0.55 to -0.08.

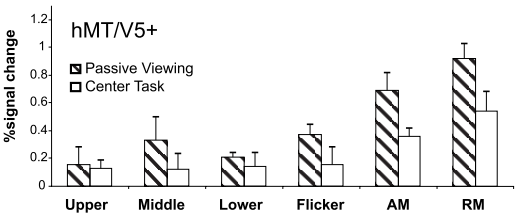

Figure 5. Attentional modulation of activity in hMT/V5+ in Experiment 2. Responses to the different conditions in Experiment 2 for the region hMT/V5+. The bars designate percent signal change of the peak response relative to baseline (see Materials and Methods). The hatched bars are activations from runs with passive viewing only, and the unhatched bars are from runs with center task. The static conditions – *upper*, *middle*, *lower*, and *flicker* – induced only low activation in hMT/V5+. In contrast, the response to *apparent motion* and *real motion* was higher, in correspondence with the motion sensitivity of hMT/V5+. The attentional modulation of the responses was very strong. In all conditions, the activity was smaller during runs with center task than during runs with passive viewing. Error bars correspond to standard errors of the mean.

Experiment 3

In a third experiment we presented a bistable apparent-motion stimulus that consisted of four blinking squares (*motion quartet*; Figure 1H). The motion quartet induces spontaneous switches between the perceptions of vertical or horizontal apparent motion without any changes in the physical characteristics of the stimulus (Neuhaus, 1930; Ramachandran & Anstis, 1985). This allows to identify activity that is closely related to the conscious perception of apparent motion (Muckli et al., 2002).

We presented a motion quartet with the two squares in the right hemifield at approximately the same locations as the apparent-motion stimuli in Experiment 1 and 2. Subjects (n = 6; five subjects from Experiment 2) continuously reported their current percept using the left and right response buttons for vertical and horizontal movement, respectively.

For Experiment 3 we calculated contrast maps that indicate higher activation in response to vertical as compared to horizontal apparent-motion perception. We found patches of activity that showed a selective increase of activity following perceptual switches from horizontal apparent motion to vertical apparent motion in all six subjects (green regions in Figures 6 and S3). These patches were located within V1 between the cortical representations of the inducing stimuli (red regions in Figures 6 and S3) consistent with the cortical representation of the vertical motion streak.

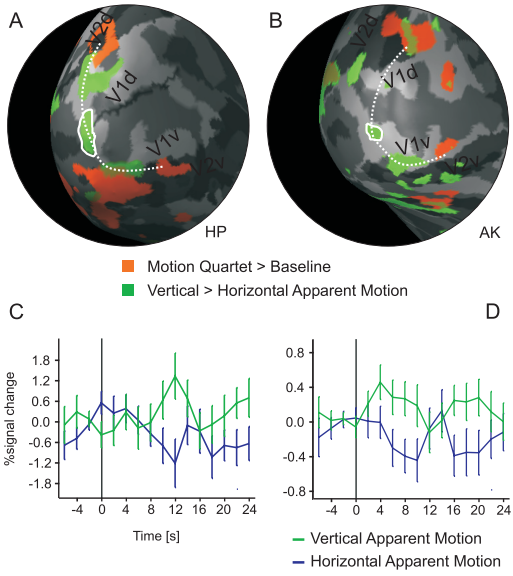

Figure 6. Results from the bistable motion quartet (Experiment 3). Medioposterior view on the inflated left occipital cortex of subject HP (A) and AK (B) (all six subjects are shown in Figure S3). Gray shading indicates the extension of V1 (light gray for V1) and the cortex curvature (dark gray: concave, light gray: convex). Activation maps show the cortical representation of the stimulated locations in red (*motion quartet* > *baseline*). Contrast maps in green indicate regions that are more active for vertical apparent motion as compared to horizontal apparent motion (ROI-based GLM at indicated locations; HP: $t(301) > 2.5$, $p < 0.02$; AK: $t(708) > 2$, $p < 0.05$). The dotted line is a spline-interpolated curve connecting the stimulated locations and the region that is more active during the perception of vertical apparent motion (this line does not necessarily indicate the path of apparent motion from Experiments 1 and 2 since stimulus parameters had to be adjusted). The solid white lines mark regions from which event-related averages were calculated. Event-related averages are shown for subject HP (C) and for subject AK (D). The time courses are aligned to the time point at which the subject indicates a switch in perception (t = 0, black line) and are shown for the time period from 4 seconds before and 24 seconds after the perceptual switch. The first perceptual period following each stimulation onset is omitted from the analysis (see Materials and Methods). Error bars correspond to standard errors of the mean. For HP the vertical percept lasted on average for 11.9 s (sd, 10.3 s), the horizontal for 13.4 s (sd, 9.2 s), for AK the vertical lasted for 14.6 s (sd, 7.1 s), and the horizontal for 16.6 s (sd, 6.7 s).

Discussion

We have shown in three experiments that there is V1 activity that correlates with the perception of long-range apparent motion. We observed activity patterns that corresponded to the expected motion streak. In ROI analyses, the apparent-motion activity was found to be significantly higher than in a flicker control condition and also unmodulated by attentional set. In an event-related design with the bistable motion quartet, the activity could be closely linked to the conscious perception of apparent motion in response to perceptual switches.

Horizontal Connections

Our results indicate that there are subregions in V1 that are active during illusory apparent-motion perception although the inducing stimuli are presented outside the receptive fields of the neurons in these regions. This spreading extra-receptive field response could be mediated by horizontal connections in V1 (Stettler et al., 2002; Jancke, Chavane, Naaman, & Grinvald, 2004). However, three arguments render it unlikely that horizontal interactions within V1 are a major source of activity along the illusory motion path. First, the *flicker* stimuli did not induce a comparable extra-receptive field response although they should have caused the same local activation as the apparent-motion-inducing stimuli. Second, the horizontal connections in V1 span only short distances that are well below the distance between the representations of the apparent-motion-inducing stimuli (Stettler et al., 2002). Third, in a motion quartet there is perceptual competition between vertical and horizontal apparent motion leading to mutually exclusive percepts. There is evidence that this competition is resolved in hMT/V5+ (Sterzer, Eger, & Kleinschmidt, 2003).

Attention and Feedback

A more likely candidate for the apparent-motion-related activity is top-down influence from higher areas (Bullier, Hupé, James, & Girard, 2001). Attention increases the blood-oxygenation-level-dependent (BOLD) signal in early visual areas including primary visual cortex (Tootell et al., 1998; Watanabe, Harner, Miyauchi, Sasaki, Nielsen, Palomo, & Mukai, 1998; Brefczynski & DeYoe, 1999; Gandhi et al., 1999; Somers et al., 1999; Slotnick, Schwarzbach, & Yantis, 2003), even in the absence of visual stimulation (Kastner et al., 1999). However, data from our control experiment show that the apparent-motion-related activation persisted when we diverted the subjects' attention away from the stimuli. Thus, apparent-motion-related activation is not solely due to spatial attention. This suggests an attention-independent but motion-specific filling-in process associated with the illusory motion percept.

The best candidate area for a possible top-down influence on V1 related to processing of apparent motion is hMT/V5+. Several studies have emphasized the important influence that feedback from higher areas has on functions of primary visual cortex (Hupé, James, Payne, Lomber, Girard, & Bullier, 1998; Bullier et al., 2001; Supèr, Spekreijse, & Lamme, 2001; Galuske, Schmidt, Goebel, Lomber, & Payne, 2002; Lee, Blake, & Heeger, 2005), and feedback from hMT/V5+ to V1 has been assigned a role in the perception of real motion and apparent motion (Yantis & Nakama, 1998; Seghier et al., 2000; Pascual-Leone & Walsh, 2001; Antal et al., 2003; Silvanto et al., 2005). Neurons in hMT/V5+ have receptive fields large enough to span the distance between the apparent-motion-inducing stimuli, and they respond to apparent motion in similar ways as to real motion (Mikami, Newsome, & Wurtz, 1986a; Goebel et al., 1998; Muckli et al., 2002). The backprojections from higher to lower cortical areas fan out and can span at least the size of their receptive fields (Salin, Girard, Kennedy, & Bullier, 1992; Salin & Bullier, 1995; Stettler et al., 2002).

We observed illusion-related activity and real-motion-related activity not only on the direct motion path but also in the periphery of the motion streak. Co-activation of more peripheral sections might be a result of feedback activity that is spreading out to larger sections in the periphery. Especially those cells that have sufficiently large receptive fields to cover both apparent-motion-inducing stimuli (16.5°) are expected to be found in more peripheral sections of higher visual areas and are therefore expected to backproject especially to peripheral parts in early visual areas.

Previous and related findings

Why was the earlier attempt of Liu et al. (2004) unsuccessful in finding apparent-motion-related activity in V1? The experimental strategy of these colleagues is quite comparable to ours in most aspects. The main difference is the stimulation material that was used: large rings inducing radial inward-outward apparent motion. The stimulation of large sections of the visual cortex might have induced a complex pattern of excitation and inhibition in directly adjacent parts of V1. Moreover, we have shown that in most subjects apparent-motion-related activity was displaced to the periphery. So we suppose that in the case of inward-outward apparent motion much of the apparent-motion-related activity might have been displaced towards the outer ring.

A number of recent studies demonstrated a close relationship between activation in primary visual cortex and conscious perception of visual stimuli. In these studies, different imaging and electrophysiological methods have been used to investigate the functional properties of V1 during binocular rivalry (Polonsky, Blake, Braun, & Heeger, 2000; Tong & Engel, 2001; Lee & Blake, 2002; Tong, 2003), perception of moving phosphenes (Pascual-Leone & Walsh, 2001; Silvanto et al., 2005), figure-ground segregation (Skiera, Petersen, Skalej, & Fahle, 2000; Supèr et al., 2001; Lamme, 2003; Supèr, van der Togt, Spekreijse, & Lamme, 2003), the 'line-motion' illusion (Jancke et al., 2004), and color filling-in (Sasaki & Watanabe, 2004). In contrast to previous results (Crick & Koch, 1995), it was found that V1 activity can be tightly linked to visual awareness. This has been supported in other experiments showing that complex features, such as motion-defined edges (Reppas, Niyogi, Dale, Sereno, & Tootell, 1997) and second-order motion (Nishida, Sasaki, Murakami, Watanabe, & Tootell, 2003; Seiffert, Somers, Dale, & Tootell, 2003), are represented as early as in V1. The new view on early visual processing has been applied to other sensory systems. Chen et al. (Chen, Friedman, & Roe, 2003) demonstrated that correlates of a tactile illusion could already be found in primary somatosensory cortex. In our study, we extended the previous findings to the domain of apparent motion.

Current findings from simultaneous fMRI and electrophysiological recordings in monkeys have suggested that the BOLD signal might be especially sensitive to changes in local field potentials (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). This could explain why the spiking activity of neurons located along the illusory motion trace has been found unchanged in earlier electrophysiological studies of V1 in macaques (Mikami et al., 1986b). Logothetis and colleagues showed that the BOLD signal is correlated with an increase in neuronal activity but further suggested that it primarily reflects the input of a cortical area and its local intracortical processing including excitatory and inhibitory interneurons (Logothetis, 2003). Our data are consistent with the interpretation that on the level of hMT/V5+ motion features are extracted from neurons with sufficiently large receptive fields to cover both apparent-motion-inducing stimuli. Feedback from hMT/V5+ could cause synaptic processes at the level of V1 that produce a BOLD response without causing major increases in spiking activity. Whether and how interactions between hMT/V5+ and V1 contribute to the perception of apparent motion remains to be investigated in future studies.

Acknowledgments

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References

Albright, T.D. (1993). Cortical processing of visual motion. *Rev. Oculomot. Res., 5*, 177-201.

Angelucci, A., Levitt, J.B., Walton, E.J.S., Hupé, J.M., Bullier, J., & Lund, J.S. (2002). Circuits for local and global signal integration in primary visual cortex. *J. Neurosci., 22*, 8633-8646.

Antal, A., Kincses, T.Z., Nitsche, M.A., & Paulus, W. (2003). Modulation of moving phosphene thresholds by transcranial direct current stimulation of V1 in human. *Neuropsychologia, 41*, 1802-1807.

Boynton, G.M., Engel, S.A., Glover, G.H., & Heeger, D.J. (1996). Linear systems analysis of functional magnetic resonance imaging in human V1. *J. Neurosci., 16*, 4207-4221.

Braddick, O.J. (1980). Low-level and high-level processes in apparent motion. *Philos. Trans. R. Soc. Lond. B Biol. Sci., 290*, 137-151.

Brefczynski, J.A., & DeYoe, E.A. (1999). A physiological correlate of the 'spotlight' of visual attention. *Nat. Neurosci., 2*, 370-374.

Bullier, J., Hupé, J.M., James, A.C., & Girard, P. (2001). The role of feedback connections in shaping the responses of visual cortical neurons. *Prog. Brain Res., 134*, 193-204.

Chaudhuri, A. (1990). Modulation of the motion aftereffect by selective attention. *Nature, 344*, 60-62.

Chen, L.M., Friedman, R.M., & Roe, A.W. (2003). Optical imaging of a tactile illusion in area 3b of the primary somatosensory cortex. *Science, 302*, 881-885.

Crick, F., & Koch, C. (1995). Are we aware of neural activity in primary visual cortex? *Nature, 375*, 121-123.

Dubner, R., & Zeki, S.M. (1971). Response properties and receptive fields of cells in an anatomically defined region of the superior temporal sulcus in the monkey. *Brain Res., 35*, 528-532.

Engel, S.A., Rumelhart, D.E., Wandell, B.A., Lee, A.T., Glover, G.H., Chichilnisky, E.J., & Shadlen, M.N. (1994). fMRI of human visual cortex. *Nature, 369*, 525.

Finlay, D., & von Grünau, M.W. (1987). Some experiments on the breakdown effect in apparent motion. *Percept. Psychophys., 42*, 526-534.

Galuske, R.A., Schmidt, K.E., Goebel, R., Lomber, S.G., & Payne, B.R. (2002). The role of feedback in shaping neural representations in cat visual cortex. *Proc. Natl. Acad. Sci. USA, 99*, 17083-17088.

Gandhi, S.P., Heeger, D.J., & Boynton, G.M. (1999). Spatial attention affects brain activity in human primary visual cortex. *Proc. Natl. Acad. Sci. USA, 96*, 3314-3319.

Gattass, R., Gross, C.G., & Sandell, J.H. (1981). Visual topography of V2 in the macaque. *J. Comp. Neurol., 201*, 519-539.

Goebel, R., Khorram-Sefat, D., Muckli, L., Hacker, H., & Singer, W. (1998). The constructive nature of vision: direct evidence from functional magnetic resonance imaging studies of apparent motion and motion imagery. *Eur. J. Neurosci., 10*, 1563-1573.

Hupé, J.M., James, A.C., Payne, B.R., Lomber, S.G., Girard, P., & Bullier, J. (1998). Cortical feedback improves discrimination between figure and background by V1, V2 and V3 neurons. *Nature, 394*, 784-787.

Jancke, D., Chavane, F., Naaman, S., & Grinvald, A. (2004). Imaging cortical correlates of illusion in early visual cortex. *Nature, 428*, 423-426.

Kastner, S., De Weerd, P., Desimone, R., & Ungerleider, L.G. (1998). Mechanisms of directed attention in the human extrastriate cortex as revealed by functional MRI. *Science, 282*, 108-111.

Kastner, S., Pinsk, M.A., De Weerd, P., Desimone, R., & Ungerleider, L.G. (1999). Increased activity in human visual cortex during directed attention in the absence of visual stimulation. *Neuron, 22*, 751-761.

Kriegeskorte, N., & Goebel, R. (2001). An efficient algorithm for topologically correct segmentation of the cortical sheet in anatomical mr volumes. *Neuroimage, 14*, 329-346.

Lamme, V.A.F. (2003). Why visual attention and awareness are different. *Trends Cogn. Sci., 7*, 12-18.

Lee, S.H., & Blake, R. (2002). V1 activity is reduced during binocular rivalry. *J. Vis., 2*, 618-626.

Lee, S.H., Blake, R., & Heeger, D.J. (2005). Traveling waves of activity in primary visual cortex during binocular rivalry. *Nat. Neurosci., 8*, 22-23.

Linden, D.E., Kallenbach, U., Heinecke, A., Singer, W., & Goebel, R. (1999). The myth of upright vision. A psychophysical and functional imaging study of adaptation to inverting spectacles. *Perception, 28*, 469-481.

Liu, T., Slotnick, S.D., & Yantis, S. (2004). Human MT+ mediates perceptual filling-in during apparent motion. *NeuroImage, 21*, 1772-1780.

Logothetis, N.K. (2003). The underpinnings of the BOLD functional magnetic resonance imaging signal. *J. Neurosci., 23*, 3963-3971.

Logothetis, N.K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature, 412*, 150-157.

Mikami, A. (1991). Direction selective neurons respond to short-range and long-range apparent motion stimuli in macaque visual area MT. *Int. J. Neurosci., 61*, 101-112.

Mikami, A., Newsome, W.T., & Wurtz, R.H. (1986a). Motion selectivity in macaque visual cortex. I. Mechanisms of direction and speed selectivity in extrastriate area MT. *J. Neurophysiol., 55*, 1308-1327.

Mikami, A., Newsome, W.T., & Wurtz, R.H. (1986b). Motion selectivity in macaque visual cortex. II. Spatiotemporal range of directional interactions in MT and V1. *J. Neurophysiol., 55*, 1328-1339.

Muckli, L., Kriegeskorte, N., Lanfermann, H., Zanella, F.E., Singer, W., & Goebel, R. (2002). Apparent motion: event-related functional magnetic resonance imaging of perceptual switches and states. *J. Neurosci., 22*, RC219 (1-5).

Neuhaus, W. (1930). Experimentelle Untersuchung der Scheinbewegung. *Arch. Gesamte Psychol., 75*, 315-458.

Newsome, W.T., Mikami, A., & Wurtz, R.H. (1986). Motion selectivity in macaque visual cortex. III. Psychophysics and physiology of apparent motion. *J. Neurophysiol., 55*, 1340-1351.

Nishida, S., Sasaki, Y., Murakami, I., Watanabe, T., & Tootell, R.B. (2003). Neuroimaging of direction-selective mechanisms for second-order motion. *J. Neurophysiol., 90*, 3242-3254.

Pascual-Leone, A., & Walsh, V. (2001). Fast backprojections from the motion to the primary visual area necessary for visual awareness. *Science, 292*, 510-512.

Polonsky, A., Blake, R., Braun, J., & Heeger, D.J. (2000). Neuronal activity in human primary visual cortex correlates with perception during binocular rivalry. *Nat. Neurosci., 3*, 1153-1159.

Ramachandran, V.S., & Anstis, S.M. (1985). Perceptual organization in multistable apparent motion. *Perception, 14*, 135-143.
Reppas, J.B., Niyogi, S., Dale, A.M., Sereno, M.I., & Tootell, R.B.H. (1997). Representation of motion boundaries in retinotopic human visual cortical areas. *Nature, 388*, 175-179.
Salin, P.A., & Bullier, J. (1995). Corticocortical connections in the visual system: structure and function. *Physiol. Rev., 75*, 107-154.
Salin, P.A., Girard, P., Kennedy, H., & Bullier, J. (1992). Visuotopic organization of corticocortical connections in the visual system of the cat. *J. Comp. Neurol., 320*, 415-434.
Sasaki, Y., & Watanabe, T. (2004). The primary visual cortex fills in color. *Proc. Natl. Acad. Sci. USA, 101*, 18251-18256.
Seghier, M., Dojat, M., Delon-Martin, C., Rubin, C., Warnking, J., Segebarth, C., & Bullier, J. (2000). Moving illusory contours activate primary visual cortex: an fMRI study. *Cereb. Cortex, 10*, 663-670.
Seiffert, A.E., Somers, D.C., Dale, A.M., & Tootell, R.B.H. (2003). Functional MRI studies of human visual motion perception: texture, luminance, attention and after-effects. *Cereb. Cortex, 13*, 340-349.
Selmes, C.M., Fulham, W.R., Finlay, D.C., Chorlton, M.C., & Manning, M.L. (1997). Time-till-breakdown and scalp electrical potential maps of long-range apparent motion. *Percept. Psychophys., 59*, 489-499.
Sereno, M.I., Dale, A.M., Reppas, J.B., Kwong, K.K., Belliveau, J.W., Brady, T.J., Rosen, B.R., & Tootell, R.B.H. (1995). Borders of multiple visual areas in humans revealed by functional magnetic resonance imaging. *Science, 268*, 889-893.
Silvanto, J., Cowey, A., Lavie, N., & Walsh, V. (2005). Striate cortex (V1) activity gates awareness of motion. *Nat. Neurosci., 8*, 143-144.
Skiera, G., Petersen, D., Skalej, M., & Fahle, M. (2000). Correlates of figure-ground segregation in fMRI. *Vision Res., 40*, 2047-2056.
Slotnick, S.D., Schwarzbach, J., & Yantis, S. (2003). Attentional inhibition of visual processing in human striate and extrastriate cortex. *NeuroImage, 19*, 1602-1611.
Smith, A.T., Singh, K.D., Williams, A.L., & Greenlee, M.W. (2001). Estimating receptive field size from fMRI data in human striate and extrastriate visual cortex. *Cereb. Cortex, 11*, 1182-1190.
Somers, D.C., Dale, A.M., Seiffert, A.E., & Tootell, R.B.H. (1999). Functional MRI reveals spatially specific attentional modulation in human primary visual cortex. *Proc. Natl. Acad. Sci. USA, 96*, 1663-1668.
Sterzer, P., Eger, E., & Kleinschmidt, A. (2003). Responses of extrastriate cortex to switching perception of ambiguous visual motion stimuli. *Neuroreport, 14*, 2337-2341.
Stettler, D.D., Das, A., Bennett, J., & Gilbert, C.D. (2002). Lateral connectivity and contextual interactions in macaque primary visual cortex. *Neuron, 36*, 739-750.
Supèr, H., Spekreijse, H., & Lamme, V.A.F. (2001). Two distinct modes of sensory processing observed in monkey primary visual cortex (V1). *Nat. Neurosci., 4*, 304-310.
Supèr, H., van der Togt, C., Spekreijse, H., & Lamme, V.A.F. (2003). Internal state of monkey primary visual cortex (V1) predicts figure-ground perception. *J. Neurosci., 23*, 3407-3414.
Tong, F. (2003). Primary visual cortex and visual awareness. *Nat. Rev. Neurosci., 4*, 219-229.
Tong, F., & Engel, S.A. (2001). Interocular rivalry revealed in the human cortical blind-spot representation. *Nature, 411*, 195-199.

Tootell, R.B.H., Hadjikhani, N., Hall, E.K., Marrett, S., Vanduffel, W., Vaughan, J.T., & Dale, A.M. (1998). The retinotopy of visual spatial attention. *Neuron, 21*, 1409-1422.

Tootell, R.B.H., Mendola, J.D., Hadjikhani, N.K., Liu, A.K., & Dale, A.M. (1998). The representation of the ipsilateral visual field in human cerebral cortex. *Proc. Natl. Acad. Sci. USA, 95*, 818-824.

Watanabe, T., Harner, A.M., Miyauchi, S., Sasaki, Y., Nielsen, M., Palomo, D., & Mukai, I. (1998). Task-dependent influences of attention on the activation of human primary visual cortex. *Proc. Natl. Acad. Sci. USA, 95*, 11489-11492.

Wertheimer, M. (1912). Experimentelle Studien über das Sehen von Bewegung. *Z. Psychol., 61*, 161-265.

Yantis, S., & Nakama, T. (1998). Visual interactions in the path of apparent motion. *Nat. Neurosci., 1*, 508-512.

CHAPTER 3

The Temporal Characteristics of Motion Processing in hMT/V5+: Combining fMRI and Neuronavigated TMS

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Abstract

Functional imaging has demonstrated the specific involvement of human middle-temporal complex (hMT/V5+) during processing of moving stimuli. Some studies applied transcranial magnetic stimulation (TMS) to investigate the causal relevance of hMT/V5+ for motion perception. Although the studies used similar visual stimuli and TMS parameters, the critical time point of functionally relevant hMT/V5+ activity differed by 100 ms and more. The present study aimed to elucidate further the temporal characteristics of motion processing in hMT/V5+ by investigating all critical time windows currently debated in the literature. In contrast to previous studies, we used TMS neuronavigation based on individual fMRI results of five participants to target hMT/V5+, applying single-pulse TMS at 24 different time windows (-50 till +200 ms relative to stimulus onset). We revealed that TMS significantly impaired motion perception when applied over hMT/V5+ at 40 to 30 ms before as well as 130 to 150 ms after onset of the moving stimuli. While the late effective time window conforms to results from previous experiments, we did not find evidence for an early time window around 0 ms that has been reported in other studies. Our neuronavigation approach enabled us to quantify the inter-individual variance in the exact location of hMT/V5+ and the respective TMS target position on the skull of the participants. Considering that shifting the TMS coil position only by a few millimeters can already lead to a complete loss of TMS effects, our study clearly demonstrates the utility of neuronavigated TMS when investigating specific neuronal effects as in the case of motion processing.

Introduction

The perception of motion represents one of the most crucial abilities of our visual system, enabling us to survive in a dynamically changing environment. A large number of electrophysiological (Albright, Desimone, & Gross, 1984; Cook & Maunsell, 2002; Diogo, Soares, Koulakov, Albright, & Gattass, 2003; Snowden, Treue, Erickson, & Andersen, 1991; Van Essen, Maunsell, & Bixby, 1981; Zeki, 1974) and functional imaging studies (Gulyas, Heywood, Popplewell, Roland, & Cowey, 1994; Heeger, Boynton, Demb, Seidemann, & Newsome, 1999; Huk, Dougherty, & Heeger, 2002; Rees, Friston, & Koch, 2000; Seiffert, Somers, Dale, & Tootell, 2003; Tootell, Reppas, Kwong, Malach, Born, Brady, Rosen, & Belliveau, 1995; Watson, Myers, Frackowiak, Hajnal, Woods, Mazziotta, Shipp, & Zeki, 1993; Zeki, Watson, Lueck, Friston, Kennard, & Frackowiak, 1991; see Orban, Van Essen, & Vanduffel, 2004 for a review) have shown that within the network of specialized regions in the visual system, the extrastriate visual area hMT/V5+, located in the occipitotemporal cortex, is specifically activated during the processing of moving stimuli.

Although likely, this evidence alone does not allow inferences on the causal role of neuronal activity in hMT/V5+ for motion perception. A causal relationship can only be inferred if a documented change of activity in hMT/V5+ causes a related change in motion perception. Neuronal activity in hMT/V5+ can be disrupted due to lesions or it can be manipulated experimentally by transcranial magnetic stimulation (TMS) in humans (Sack & Linden, 2003) or cooling in animals (Hupé, James, Girard, Lomber, Payne, & Bullier, 2001). Several lesion (Baker, Hess, & Zihl, 1991; Newsome & Paré, 1988; Vaina & Cowey, 1996; Zihl, von Cramon, & Mai, 1983) and TMS studies (Anand, Olson, & Hotson, 1998; Beckers & Hömberg, 1992; Beckers & Zeki, 1995; d'Alfonso, van Honk, Schutter, Caffé, Postma, & de Haan, 2002; Hotson, Braun, Herzberg, & Boman, 1994; Hotson & Anand, 1999; Walsh, Ellison, Battelli, & Cowey, 1998) have confirmed a causal relation between hMT/V5+ activity and performance on visual motion tasks. The demonstration that TMS over hMT/V5+ can also disrupt the storage and perception of the so-called motion after-effect (Théoret, Kobayashi, Ganis, Di Capua, & Pascual-Leone, 2002; see also Antal, Varga, Nitsche, Chadaide, Paulus, Kovács, & Vidnyánszky, 2004) and even produce moving phosphenes (Antal, Kincses, Nitsche, & Paulus, 2003; Antal, Nitsche, Kincses, Lampe, & Paulus, 2004; Campana, Cowey, & Walsh, 2002; Stewart, Battelli, Walsh, & Cowey, 1999) complements the evidence that this area is functionally relevant for the processing of moving stimuli.

The systematic use of single-pulse TMS (spTMS) with its high temporal resolution in the millisecond range allows not only the identification of the functional relevance of a particular brain region but also the assessment of the exact time point at which this neuronal activity is critical. Accordingly, spTMS has been used to induce transient deficits in visual motion detection (Beckers & Hömberg, 1992). The authors displayed a pattern of randomly moving dots and observed a modulation of motion detection when stimulating hMT/V5+ within a time window of 10 ms before and 10 ms after stimulus onset. The magnetic stimulation of area hMT/V5+ selectively impaired motion perception without interfering with basic recognition of the stimuli or color perception in a control task. A similar study replicated the general result but identified as the critical time window for the impairment of motion detection the interval from 100 to 150 ms after stimulus onset (Hotson et al., 1994). On the basis of further studies on the temporal aspects of effective TMS in visual processing, Beckers and

Zeki (1995) speculated that there might be two different visual pathways to area hMT/V5+. Signals would be relayed to hMT/V5+ both directly from the thalamus and indirectly via V1. This might account for the different time windows identified by Beckers and colleagues (Beckers & Hömberg, 1992; Beckers & Zeki, 1995) and Hotson et al. (1994).

A complementary or alternative interpretation of the differing results on critical time windows in motion processing is that TMS affected different brain regions in different studies. All of the aforementioned spTMS studies were limited in their spatial accuracy in that they localized the target site for TMS merely on the basis of an anatomical-landmark criterion. The authors of these studies argued that there are several lines of evidence suggesting that a site 5 cm lateral and 3 cm dorsal to the inion would overlie hMT/V5+. The main argument for this assumption was that imaging studies had demonstrated the correspondence of those coordinates with hMT/V5+ (Watson et al., 1993; Zeki et al., 1991). Hence, these spTMS studies simply used the scalp position based on the anatomical landmarks in every participant, assuming that the cranial coordinates would generally identify the appropriate stimulation site for hMT/V5+ and that the effects of inter-individual variance in anatomical and functional organization are negligible. Yet, Watson et al. (1993) also demonstrated that the position of area hMT/V5+ itself is not constant from one individual to the next and can vary by as much as 27 mm in the left, and 18 mm in the right hemisphere.

An earlier attempt to account for intersubject variability in determining the stimulation site for MT (d'Alfonso et al., 2002) was based on the individual interference maps obtained by TMS. In their procedure, the center of a two-dimensional matrix of 3x3 cm (nine points) was placed over the T5 electrode position, according to the international 10-20 EEG system. Each of the nine points was stimulated for 10 different delays, while participants performed a motion-direction discrimination task. Their method of localizing hMT/V5+ used the center-of-gravity position and thus provided an individual map of functional activity in the hMT/V5+ area. Yet, as the authors themselves acknowledged, the most accurate method of localizing the stimulation site for TMS would rather be based on the individual activation map of every participant revealed by functional imaging.

In this study, we used functional magnetic resonance imaging (fMRI) to precisely map the area hMT/V5+ in every single participant. Based on this individual functional activation map, we neuronavigated the TMS coil for magnetic stimulation to the appropriate cranial coordinates, using a frameless stereotaxic co-registration system developed by our group. We applied spTMS at 24 different time intervals, covering all critical time windows that are debated in the literature. In particular, our aim was to determine whether the motion perception is disrupted by hMT/V5+ stimulation during the very early (around stimulus onset) or during the later period (around 150ms) and whether both time windows might be critical in the same individuals.

Methods

Participants

Five volunteers (mean age = 29.2 years; range = 25 to 37 years) participated in the study. All participants were right-handed and had normal or corrected-to-normal (N = 1) vision, and had no history of neurological or psychiatric disorder. The participants were informed about MRI and TMS and received a questionnaire to check for potential health risks and contraindications. Volunteers gave their informed consent

after being introduced to the procedure. The experiments were conducted in accordance with the Declaration of Helsinki.

Overall Study Design

In our study, we experimentally combined the methods of functional and anatomical MRI with TMS. This approach enabled us to define the site for TMS stimulation based on the individual fMRI measurements and to use a neuronavigation device to guide the TMS coil to the respective target locations. Participants were tested in six separate sessions: In the first session, functional and anatomical MRI measurements were obtained from all participants. The data were used to localize hMT/V5+ and to co-register an anatomical reconstruction of the participant's head with stereotaxic data recorded with an ultrasound digitizer (see below for details). In the second session, psychophysical thresholds were determined for the random-dot paradigm in individual participants and surface points from the participant's head were recorded with a digitizer. In the four TMS sessions, participants were stimulated with single-pulse TMS while they performed the random-dot task.

MRI Measurements

Stimuli

Stimuli were generated with a custom-made program based on the Microsoft DirectX library and back-projected onto a frosted screen with a liquid-crystal-display projector. Participants viewed the screen through a mirror fixed on the head coil. Two stimulus conditions were used to identify hMT/V5+: (1) 400 white dots moving radially outward on a dark screen (visual field, 30 x 23°; dot size, 0.06 x 0.06°; dot velocity, 3.6–14.4°/sec), and (2) 400 stationary white dots with the same stimulus parameters as in condition (1). The moving-dot stimulus is known to produce strong activation in hMT/V5+, in contrast to stationary dots (Goebel, Khorram-Sefat, Muckli, Hacker, & Singer, 1998; Rees et al., 2000; Tootell et al., 1995).

Design

The two experimental conditions (moving and stationary dots) were presented alternately in blocks of 16.6 s. The conditions were always separated by a fixation period of the same length. Three blocks of moving dots and two blocks of stationary dots were used. Participants were asked to fixate and be attentive during the whole measurement. Eye movements were not monitored during MR imaging.

MR Imaging

Functional MRI was done on the 1.5 Tesla Siemens Magnetom Vision MR tomograph (Siemens, Erlangen, Germany) at the University Hospital, Frankfurt am Main, Germany, or the 3 Tesla Siemens scanner at the Brain Imaging Center Frankfurt, Frankfurt am Main. For the scans at 1.5 T, a gradient-recalled echo-planar-imaging (EPI) sequence was used with the following parameters: 16 slices, oriented approximately parallel to the calcarine sulcus; TR, 2081 msec; TE, 60 msec; FA, 90°; FOV, 210 mm, in-plane resolution, 3.44 x 3.44 mm, slice thickness, 4 mm; gap thickness, 0.4 mm. At 3 T, parameters were: 34 slices; TR, 2080 msec; TE, 30 msec; FA, 85°; FOV, 210 mm, in-plane resolution, 3.3 x 3.3 mm, slice thickness, 3 mm; gap thickness, 0.3 mm. In addition, a high-resolution T1-weighted anatomical scan was acquired using a Siemens fast low-angle-shot (FLASH; Siemens Vision scanner) or magnetization-prepared rapid-acquisition gradient-echo (MPRAGE; Siemens Trio scanner) sequence.

MRI Data Analysis

Data were analyzed using the BrainVoyager 4.9 and BrainVoyager QX 1.4 software package (BrainInnovation, Maastricht, The Netherlands). The first four volumes of each scan were discarded to allow for T1 saturation. Preprocessing of the functional data included the following steps: (1) three-dimensional motion correction using the Levenberg-Marquardt algorithm, (2) linear-trend removal, and temporal high-pass filtering at 0.01 Hz, (3) slice-scan-time correction with sinc interpolation. The statistical analysis was performed with multiple linear regression. For every voxel, the time course was regressed on a set of dummy-coded predictors representing the experimental conditions. The predictor time courses (box-car functions) were convolved with a gamma distribution to account for the shape and delay of the hemodynamic response (Boynton, Engel, Glover, & Heeger, 1996).

Co-registration of Stereotaxic and MRI Data

Stereotaxic data for the localization of the TMS stimulation site were recorded with the electrode positioning system CMS30P (zebris, Tübingen, Germany). This system consists of several miniature ultrasound transmitters, which are attached to the participant's head as well as the TMS coil. These ultrasound markers continuously transmit ultrasonic pulses to a receiving sensor device. The measurement of the relative spatial position of these transmitters in 3-D space is based on the travel time of the transmitted ultrasonic pulses to three microphones built into the receiving sensor. In a next step, local spatial coordinate systems are created by linking the relative raw spatial position of the ultrasound senders to a set of fixed additional landmarks on the participant's head. The specification of these fixed landmarks is achieved via a digitizing pen that also hosts two transmitting ultrasound markers in order to measure its relative position in 3-D space. The three anatomical landmarks we used to define the local coordinate system were the nasion and the two incisurae intertragicae. The system now provides topographic information of the head ultrasound transmitters relative to a participant-based coordinate frame. Similarly, the TMS coil also hosts a set of ultrasound transmitters whose relative spatial positions are linked to fixed landmarks specified on the coil in order to calculate another local coordinate system. After having defined the local spatial coordinate system for the participant's head and the TMS coil in real 3-D space, these coordinate systems have to be co-registered with the coordinate system of the MR space. For TMS-fMRI co-registration, the same landmarks digitized on the participant's head are specified on the head representation (mesh) of the participant in the fMRI software. Hence, using the BrainVoyager software, the anatomical landmarks were identified in the MRI scan of the participant's head and co-registered with the coordinates from the digitizer. As an additional constraint for the co-registration, a set of points covering the whole head were recorded from each participant. To correct for measurement errors (MRI and ultra-sound distortions), an algorithm fitted the additionally recorded surface points to the outer boundary of the MRI head reconstruction. After the landmarks specified on the real head are co-registered with those on the mesh head, events occurring around the head of the participant in real space are registered online and visualized in real-time at correct positions relative to the participant's anatomical reconstruction of the brain. By superimposing the functional data on the anatomical reconstruction of the brain, the TMS coil can be neuronavigated to a specific anatomical and/or functional activation area of every participant. TMS neuronavigation was based on data in AC-PC space (rotating the cerebrum into the anterior commissure – posterior commissure plane) in order to avoid any additional

transformations that could distort the correspondence between MRI and stereotaxic points.

Although the described fMRI-based TMS neuronavigation represents the optimal methodological approach for positioning the TMS coil relative to an individual fMRI activation cluster, it should not be neglected that the spatial resolution of localized TMS is still hampered by the spatial distribution of the applied magnetic field itself. Hence, while the full digitization of the received sonic signals during the fMRI-TMS co-registration procedure guarantees a high measuring accuracy in the millimeter range in terms of exact TMS coil positioning, the spatial distribution of the applied TMS pulse still limits the accuracy of magnetic brain stimulation. This latter limitation in spatial accuracy is solely defined by the specific geometry of the used TMS coil and can only partly be addressed by TMS neuronavigation. Nonetheless, it has been shown that despite the limited spatial resolution of the applied magnetic field, a shift of the TMS coil position by only a few millimeter can already result in a complete loss of the TMS-induced behavioral effect (Beckers & Hömberg, 1992; d'Alfonso et al., 2002).

Functional MRI data of individual participants were used to localize hMT/V5+ according to standard criteria (Muckli, Kriegeskorte, Lanfermann, Zanella, Singer, & Goebel, 2002). A contrast between the motion and the static condition was computed (in participant P3, the contrast motion vs. static was too weak; we therefore used motion vs. baseline). The known anatomical landmarks and Talairach coordinates were used as additional constraints for the identification of hMT/V5+ (Dumoulin, Bittar, Kabani, Baker, Jr., Le Goualher, Pike, & Evans, 2000; Watson et al., 1993). The TMS stimulation site for hMT/V5+ was defined as the surface point whose normal vector intersected the hMT/V5+ cluster (see Fig. 2 and 3). The normal vector was approximated locally using neighboring surface points. In addition, a control location was defined at a distance of 4 cm in the parasagittal plane superior to the individual hMT/V5+ surface point (Fig. 3). This site was chosen as a control site because it was sufficiently close to the hMT/V5+ site to mimic the non-neuronal effects of TMS (coil click and skin stimulation) while the stimulated brain area did not show any motion-specific activation.

TMS Measurements

TMS Apparatus and Stimulation Parameters

Biphasic TMS pulses were applied with a figure-of-eight coil (MC-B70, the inner and outer radii of the two coil loops are 1.2 and 5.4 cm, respectively) and a Medtronic-Dantec MagPro stimulator (Medtronic Functional Diagnostics A/S, Skovlunde, Denmark; maximum stimulator output, 2 T). The coil was fixed on a tripod and placed tangentially on the skull with a custom-made coil holder. The handle was oriented parallel to the horizontal plane pointing towards the occiput. The coil position was monitored on-line with the ElGuide (zebris, Tübingen, Germany) or BrainVoyager software and adjusted to the respective target location. Single-pulse TMS was applied at 70% of maximum stimulator output. To avoid computer monitor artifacts and to provide accurate timing, the TMS pulses were applied in the vertical refresh period of the cathode-ray-tube (CRT) monitor.

Stimuli

Stimuli were generated with a custom-made program based on the Microsoft DirectX library and presented on a CRT monitor. The distance between the participants' eyes and the monitor was 47 cm. The stimulus consisted of a frameless square window of

moving random dots located to the right of the fixation cross at an eccentricity of 11.0° visual angle (distance from the fixation cross to the center of the square); the side length of the square was 7.4°. Comparable stimuli have been used in previous TMS, neurophysiological, and neuropsychological studies of motion perception (Baker et al., 1991; Beckers & Hömberg, 1992; Beckers & Zeki, 1995; Hotson et al., 1994; Newsome & Paré, 1988). The random-dot moving pattern was presented for five consecutive frames, corresponding to an approximate presentation duration of 50 ms (refresh rate, 100 Hz). During the first stimulus frame, one hundred white dots (0.15° visual angle) were presented at random positions in the presentation window. For the following frames, a subset of points was displaced coherently either in the horizontal direction (right and left) or, in separate runs, in the vertical direction (up and down). The displacement corresponded to a speed of 9.0°/s. To avoid strong local motion cues, the subset of coherently moving dots was randomly selected for each frame separately, i.e., previous movement of a dot had no predictive value for subsequent movement. Points that were not selected for coherent displacement were redistributed randomly inside the window. In case a coherently moving dot was projected to a position outside the window, the dot was inserted at the opposite side. The percentage of coherent dots was adjusted individually in a preceding psychophysical session.

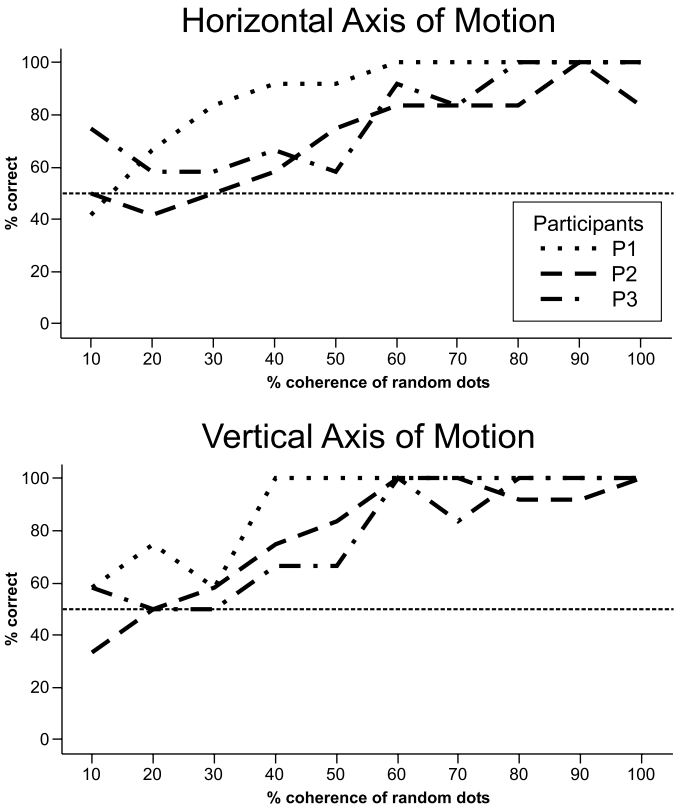

Figure 1. Performance for three out of five participants in the random-dot task. In separate trials, vertical (up and down) and horizontal motion (left and right) were tested using the Method of Constant Stimuli. At low coherence, performance dropped to chance levels (indicated with the dashed horizontal lines). At coherences of 40% to 60%, participants' performance reached almost perfect levels.

Psychophysics Session

The goal of the preliminary psychophysics was to determine an adequate coherence level in the random-dot paradigm for individual participants. In three participants, we used the method of constant stimuli with coherence levels ranging from 10% to 100%. For each coherence level and each of the four motion directions (up, down, left, and right), participants performed six trials, resulting in 240 trials overall. The trials were divided into two blocks with vertical motion and two blocks with horizontal

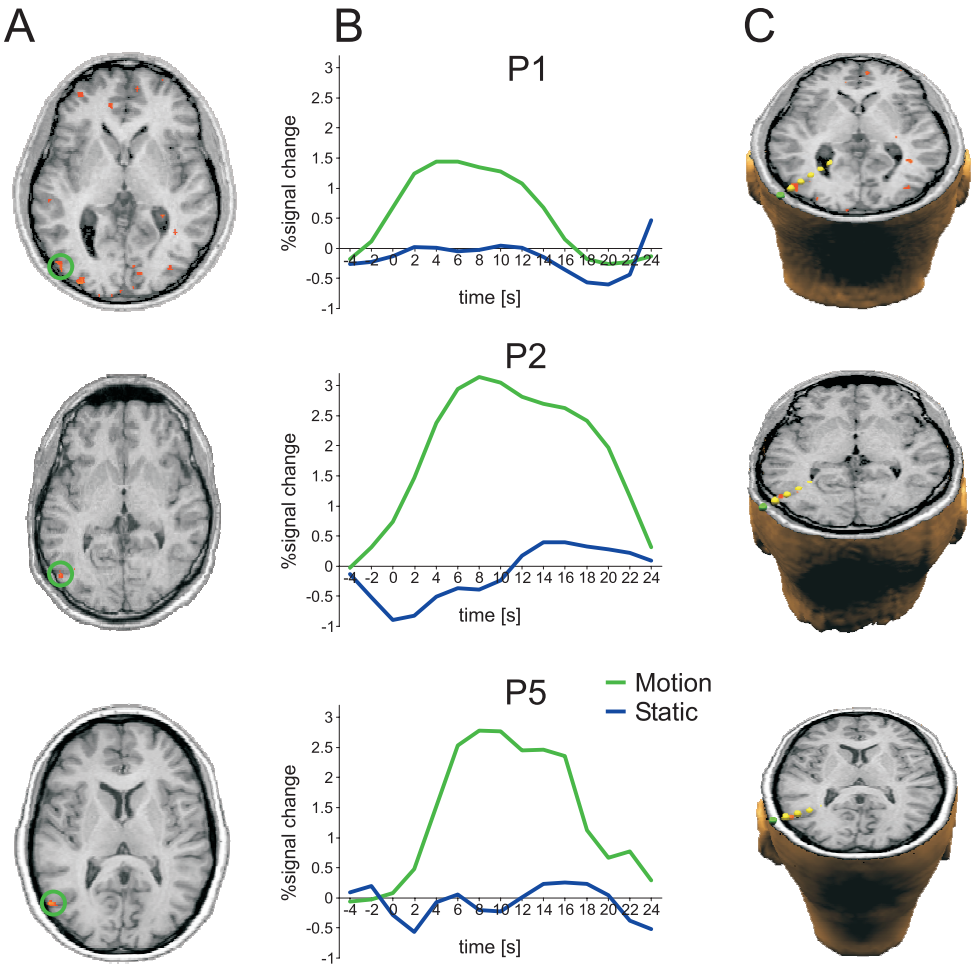

Figure 2. Location of left hMT/V5+ and the corresponding TMS site in three out of five participants. (A) Axial slices at the level of hMT/V5+ (marked with a green circle). Voxels with significant activation (p (uncorrected) < 0.005) in response to random-dot motion vs. static dots (see Materials and Methods) are marked in false colors. (B) BOLD time courses from hMT/V5+. The response to coherently moving dots (green line) is markedly larger than the response to static dots (blue line). (C) Axial slices through head reconstructions showing the hMT/V5+ stimulation site (green sphere) relative to motion-specific activation. The yellow spheres visualize the orientation of the TMS coil. The imagined line through the spheres corresponds to the normal vector originating from the TMS focus (distance between spheres is 1 cm).

motion. The stimulus-onset asynchrony between trials was four seconds. Participants had to indicate the movement direction accurately and as quickly as possible pressing one of two keys (either up and down, or right and left). Reaction times and button presses were recorded by the stimulation program. For the TMS session, a coherence level was selected at which participants obtained at least 90% correct responses. For two participants, we used an abbreviated procedure to find an appropriate coherence level. We started at a coherence of 80% and adjusted the level in steps of 5% until criterion was reached (90% correct responses).

TMS Sessions

Participants were tested with single-pulse TMS on four different days (split evenly between vertical and horizontal random-dot patterns). On each day, they performed a total of 480 trials in eight blocks of 60 trials. In four of the eight blocks participants were stimulated at hMT/V5+, in the other four blocks at the control site. The sequence of stimulation sites was counterbalanced across participants. For each motion axis, 24 different stimulus pulse asynchronies (SPA = TMS-pulse onset minus stimulus onset in milliseconds) were tested. The SPAs ranged from -50 ms to 200 ms in steps of 10 ms. The SPAs of 50 ms and 70 ms were omitted to reduce the overall number of TMS pulses, since no effects had been reported in previous studies at or near these intervals (Beckers & Hömberg, 1992; Hotson et al., 1994).

Table 1. Talairach coordinates of hMT/V5+ in the left hemisphere of individual participants.

Participant	x	y	z
P1	-45	-76	6
P2	-50	-70	2
P3	-46	-72	3
P4	-42	-75	7
P5	-52	-65	10

Notes. Talairach conventions: x - left to right, y - back to front, z - bottom to top

Before the first TMS session started, coherence levels of the random-dot stimuli were again adjusted to assure high performance levels for the task. Participants had to complete blocks of 24 trials without TMS until they reached an accuracy of 90% or higher, starting with the coherence level that had been determined in the preliminary psychophysics. When participants failed to reach the desired performance level in two subsequent blocks, the coherence level was raised in 5% steps. The resulting coherence level was used for all following measurements.

Table 2. Distance from site of TMS stimulation (hMT/V5+) to the inion of each individual participant in mm.

Participant	x	y	z	Euclidian Distance (mm)
P1	54	20	34	67
P2	63	26	37	78
P3	61	35	21	73
P4	55	20	41	71
P5	63	33	40	82

Notes. Coordinates: x - left to right in the ACPC plane, y - back to front in the ACPC plane, z - bottom to top orthogonal to the ACPC plane

Data Analysis

The logic of our study was to investigate a small number of participants with maximum precision and a high number of trials. We analyzed our single-trial count data with a hierarchical log-linear analysis (Howell, 2004). A log-linear analysis allows to handle multi-way contingency tables and to test for main and interaction effects. It uses an iterative procedure to generate maximum-likelihood estimates. The variables of interest in our analysis were axis of motion (horizontal vs. vertical), TMS

stimulation site (hMT/V5+ vs. control), SPA (24 intervals), and correctness of responses (correct vs. incorrect). The data were analyzed with the HILOGLINEAR algorithm of the SPSS 12.0 software package (SPSS Inc., Chicago, IL, United States of America). The algorithm was applied with backward elimination of variables and an elimination criterion of p = .05. The maximum number of iterations was set to 20. To identify SPAs at which the number of correct responses was reduced at hMT/V5+ relative to the control site, we performed post-hoc chi-square tests for the 24 SPAs with Bonferroni correction for multiple comparisons.

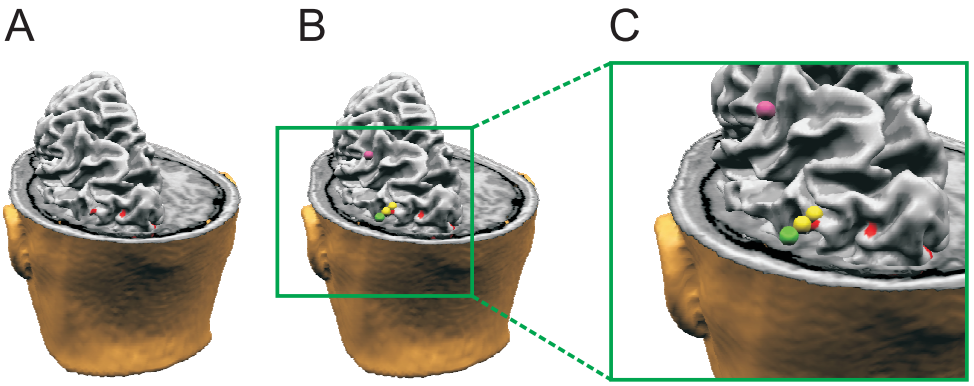

Figure 3. Stimulation sites relative to left hMT/V5+ and the sulcal anatomy in participant P1. (A)-(C) Reconstruction of the head as well as the white-/gray-matter boundary of participant P1. Areas with motion-specific responses are marked in red. (B) TMS site targeting hMT/V5+ is indicated with a green sphere. The yellow spheres visualize the orientation of the TMS coil (normal vector originating from the TMS focus; distance between spheres is 1 cm). The magenta sphere is located at the stimulation site for the control condition. (C) Close-up view of the hMT/V5+ section marked in (B).

Results

Co-registration of fMRI and Stereotaxic Data

We used a co-registration procedure to target hMT/V5+ based on previously measured fMRI data from individual participants. This neuronavigation approach allowed us to accommodate interindividual differences in hMT/V5+ localization and to validate independently the appropriateness of the TMS stimulation site. The average Talairach coordinates of left hMT/V5+ for our five participants were -47, -72, 6; the centers of mass are provided in Table 1. The maximal Euclidean distance between Talairach coordinates of our participants was 14 mm. The coordinates were in agreement with previous reports (Goebel et al., 1998; Muckli et al., 2002; Tootell, Reppas, Dale, Look, Sereno, Malach, Brady, & Rosen, 1995; Watson et al., 1993).

In other studies investigating motion processing in hMT/V5+ (Beckers & Hömberg, 1992; Beckers & Zeki, 1995; Hotson et al., 1994), the location of the TMS stimulation site was defined relative to the inion, an anatomical landmark at the back of the head. To compare our stimulation sites to these studies, we computed the distance of the hMT/V5+ surface point to the inion (Table 2). On average, the TMS stimulation site

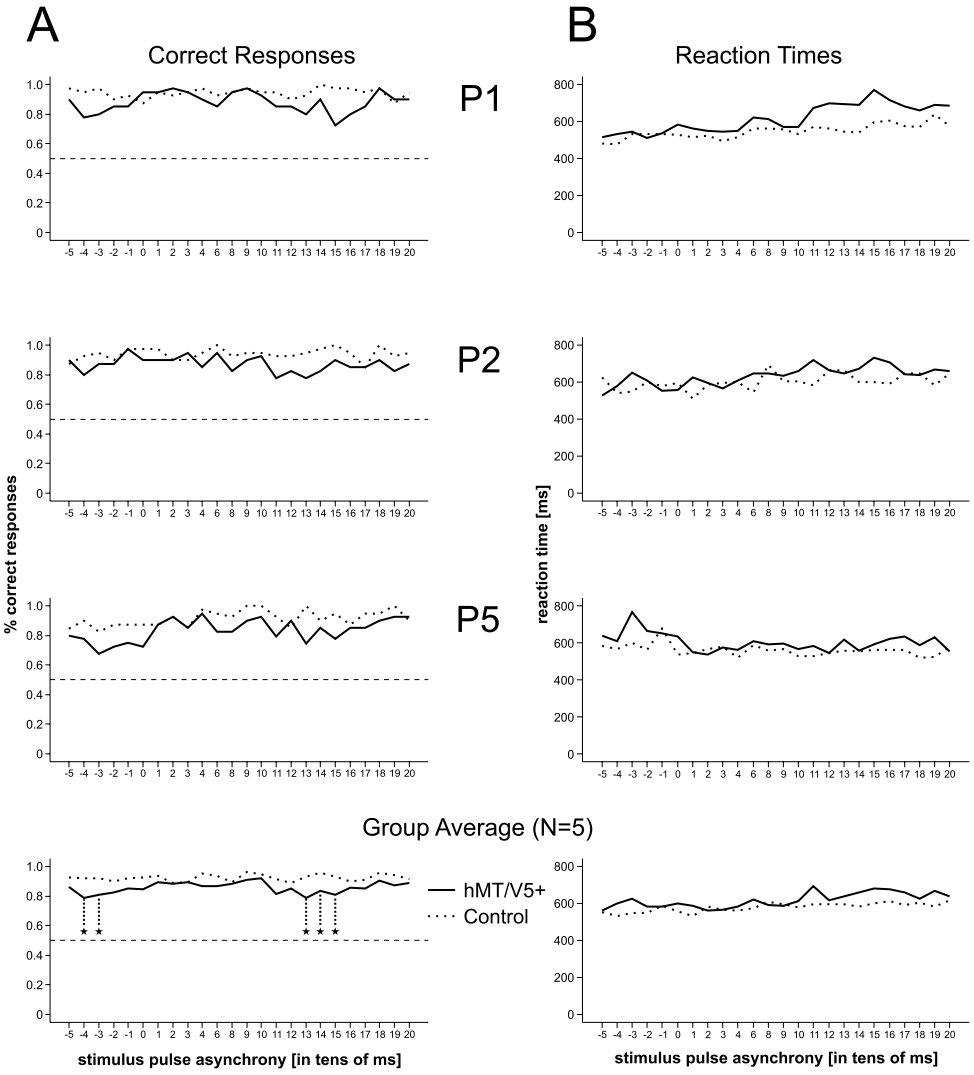

Figure 4. Percent correct responses and reaction times for three out of five participants and average values. (A) Percent correct responses of participants P1, P2, and P5, and the group average value (N = 5) for the 24 different stimulus-pulse asynchronies (SPA). The horizontal dashed lines indicate performance at chance level. The performance of participants is impaired for stimulation over hMT/V5+ (green line) compared to stimulation over the control site (blue line). There is a selective reduction of correct responses in two major time windows in all participants: an early interval at -40 to -20 ms SPA and a late window around 110-160 ms SPA. Although the exact time point of maximal effectiveness differs between participants, we found significant average differences between conditions in both time intervals (-40 and -30 ms as well as 130-150 ms; marked with an asterisk). There were no significant effects at any other time window. (B) Reaction times do not show a consistent trend across participants.

for hMT/V5+ was located 59 mm left to the midsagittal plane, 27 mm anterior to the inion, and 35 mm above the AC-PC plane, resulting in an Euclidean distance of 74

mm. This corresponds to the guidelines described in the literature, according to which hMT/V5+ is located 5-6 cm lateral to and 3-4 cm above the inion (Beckers & Hömberg, 1992; Beckers & Zeki, 1995; Hotson et al., 1994; Stewart et al., 1999). Still, the location of the optimal TMS stimulation site for hMT/V5+ can vary considerably between participants. In our group, the maximal difference for the position relative to the inion was 15 mm. Although the spatial resolution of TMS is limited due to the non-focal nature of the magnetic field, a shift of 15 mm can lead to the complete loss of TMS effects (Beckers & Hömberg, 1992; d'Alfonso et al., 2002).

Psychophysics

Participants were tested with the random-dot paradigm in a preliminary session to find a coherence level at which they showed almost perfect performance. In a range from 10% to 60% coherence, performance increased almost linearly in all participants, leveling off at higher coherences with perfect performance (Fig. 1). For our purpose, threshold was defined as the coherence level with a performance at or above 90%. In the firtime intervals between stimulus onset and the TMS pulse, ranging from 50 ms before to 200 ms after stimulus onset. The same set of intervals was also tested with TMS at the control site in parietal cortex. All participants showed a decrease of correct responses for TMS at hMT/V5+ relative to the control condition (Fig. 4A). The reductions were not evenly distributed among the time intervals. There were distinct time periods with reductions of up to 20%. For other time periods, there was no difference between the hMT/V5+ and the control condition. In two time windows, -40 to -20 ms and 110 to 160 ms, there was a consistent effect in all five participants. The reaction-time data did not show a corresponding effect across participants (Fig. 4B).

For statistical analysis of the correct responses, we performed a hierarchical log-linear analysis with the following factors: direction axis (horizontal vs. vertical), stimulation site (hMT/V5+ vs. control), stimulus-TMS asynchrony (from -50 to 200 ms), and correctness of response (correct vs. incorrect). Although the number of incorrect responses was higher for horizontal vs. vertical motion (interaction 'direction axis' x 'correctness of response'; $\chi^2(1) = 11.601$, $p < 0.001$), the interactions of the factor 'direction axis' with other factors were insignificant ($p > 0.25$), meaning that the pattern of results was similar for the vertical and horizontal motion directions. The final model of the log-linear analysis included two additional interaction terms: 'condition' × 'correctness of response' ($\chi^2(1) = 113.165$, $p < 0.001$) as well as 'stimulus-TMS asynchrony' × 'correctness of response' ($\chi^2(23) = 55.759$, $p < 0.001$). As expected, this implies that the percentage of correct responses was significantly different for the two TMS conditions, as well as for different stimulus-TMS asynchronies. The three-way interaction 'stimulus-TMS asynchrony' × 'condition' × 'correctness of response' showed a trend towards significance ($\chi^2(1) = 32.549$, $p = 0.09$).

To identify the time intervals in which the number of correct responses was reduced in the hMT/V5+ condition relative to the control site, we performed post-hoc chi square tests with Bonferroni correction for the different stimulus-TMS asynchronies. With a conservative threshold of p (Bonferroni) < 0.05, we found five time intervals with a significant reduction of correct responses: In the early time window, the effect was significant at -40 and -30 ms; for the late time window, the differences at 130, 140, and 150 ms reached significance.

Discussion

We show that targets for TMS application can be reliably selected on the basis of individual activation patterns from an fMRI experiment. Area hMT/V5+ was identified in individual participants using a motion-mapping paradigm. Anatomical and functional MRI data were co-registered with stereotaxic data from the participants' heads, and TMS was applied to the individually defined stimulation sites. TMS at hMT/V5+ but not at a parietal control site led to a significant reduction of correct motion discriminations in an early (-40 to -30 ms) and a late (130 to 150 ms) time window. Motion axis (vertical vs. horizontal) did not have a significant influence on the TMS effects.

Our data confirm that hMT/V5+ is of special relevance for the visual processing of moving stimuli. Earlier studies in macaques and humans have shown that lesions in hMT/V5+ produce severe deficits in motion perception (Baker et al., 1991; Newsome & Paré, 1988; Zeki et al., 1991; Zihl et al., 1983). We produced 'virtual lesions' (Cowey & Walsh, 2001) with spTMS in a time-dependent manner. In contrast to earlier TMS studies (Anand et al., 1998; Beckers & Hömberg, 1992; Beckers & Zeki, 1995; d'Alfonso et al., 2002; Hotson et al., 1994), we were able to explicitly target hMT/V5+ with a neuronavigation device based on fMRI data from individual participants. This is an important methodological improvement because, first, the exact location of hMT/V5+ can vary considerably between participants (Watson et al., 1993) and, second, moving phosphenes, which are used to identify hMT/V5+ functionally, can be produced only in a small percentage of participants (Pascual-Leone & Walsh, 2001). Moreover, moving phosphenes as a location criterion are not specific for hMT/V5+ since they also result from stimulation at other cortical sites (Fernandez, Alfaro, Tormos, Climent, Martínez, Vilanova, Walsh, & Pascual-Leone, 2002). In addition, there is another motion-processing region (kinetic occipital; Orban, Dupont, De Bruyn, Vogels, Vandenberghe, & Mortelmans, 1995) in the vicinity of hMT/V5+, which might be relevant for direction discrimination in random-dot patterns and could accidentally be targeted in TMS studies investigating hMT/V5+.

In addition to the effective time window at 130-150 ms, we found an early decrement of performance at -40 to -30 ms SPA for stimulation over hMT/V5+. If one assumes that the impact of TMS is limited to milliseconds after TMS onset (Walsh & Cowey, 2000) and takes into account the response latencies of cells in the visual cortex (Nowak, Munk, Nelson, James, & Bullier, 1995), this is most likely a non-neuronal effect that is nevertheless specific to stimulation at hMT/V5+. The effect occurs in a time window in which previous studies have described decreased performance due to reflex blinking of the eyelids (Amassian, Cracco, Maccabee, Cracco, Rudell, & Eberle, 1998; Beckers & Hömberg, 1991; Corthout, Hallett, & Cowey, 2003). We did observe in our experiments that stimulation at hMT/V5+ led to muscle twitches with a higher probability than at the parietal control site. This, in turn, could have increased the probability of blinks, which interfered with the initial processing of the visual stimulus.

Previous experiments that have studied the relevance of hMT/V5+ for processing of random-dot patterns with TMS showed mixed and partly contradictory results (Anand et al., 1998; Beckers & Hömberg, 1992; Beckers & Zeki, 1995; d'Alfonso et al., 2002; Hotson et al., 1994). Two studies found a disruptive effect on motion perception with an SPA around 0 ms (Beckers & Hömberg, 1992; Beckers & Zeki, 1995), while others reported an effective SPA of 100 to 150 ms (Anand et al., 1998; Hotson et al., 1994; see also Walsh, Ellison, Ashbridge, & Cowey, 1999). In one study, the TMS effects were topographically specific to one or a few stimulation sites

but showed mixed results in terms of the temporal distribution (d'Alfonso et al., 2002). Beckers and Hömberg (1992) tested both the early (0 ms) and late (100-150 ms) time windows in the same experiment but only found a significant impairment around 0 ms and no effect for 100-150 ms. It is unclear how these diverging results can be explained. The parameters used by Hotson et al. (1994) were different from those used in the experiments of Beckers and colleagues (Beckers & Hömberg, 1992; Beckers & Zeki, 1995). In the latter studies, the size of the random dots as well as the size of the presentation window were markedly smaller, and the window was presented at less eccentric locations in the visual field. But it is unlikely that these factors would shift the relevant time window by 100 to 150 ms, thereby fundamentally changing the temporal dynamics of stimulus processing.

In contrast, our own data indicate that the functionally critical time point of specific neuronal activity in hMT/V5+ during motion perception lies between 130-150 ms following stimulus onset. Thus, our results confirm the relevance of the late time window but not of the early window around 0 ms (the first time window at -40 to -30 ms revealed in our study is clearly separate from the debated 0-ms delay). Our data are in good accordance with MEG results measuring the temporal pattern of neuronal activity during motion processing (Ahlfors, Simpson, Dale, Belliveau, Liu, Korvenoja, Virtanen, Huotilainen, Tootell, Aronen, & Ilmoniemi, 1999; Scherg, Linden, Muckli, Roth, Drüen, Ille, Linek, Zanella, Singer, & Goebel, 1999). By using an fMRI-guided MEG source analysis, Ahlfors et al. (1999) revealed an onset latency of hMT/V5+ activation at around 130 ms with a first peak at around 150-180 ms after stimulus onset. However, other combined EEG/MEG results (ffytche, Guy, & Zeki, 1995) suggest two activation peaks depending on the speed of the motion stimulus. In this study the neuronal response to faster moving stimuli (22 degrees/s) occurred at around 50 ms, while the response to slower moving stimuli (< 6 degrees/s) occurred later in time. The authors speculated that the faster moving stimuli might be processed via a non-sequential parallel input to hMT/V5+, which by-passes V1 (dynamic parallelism). However, although this study showed that stimulus speed can have a strong impact on neuronal response latencies; we could not find any evidence for a functionally critical time point representing this parallel visual motion input to hMT/V5+. Although one might argue that our stimuli were not moving fast enough (9 degrees/s) to evoke the earlier neuronal response, the speed of our motion stimuli did not differ from those of Beckers and colleagues and thus cannot account for the contradictory finding between the different TMS studies.

Area hMT/V5+ is not the only cortical region implicated in the processing of moving patterns. Other prominent motion-selective regions are V3A and KO (Orban et al., 1995; Rees et al., 2000; Tootell et al., 1997; for review see Culham et al., 2001). Their motion selectivity is not as pronounced as that seen in hMT/V5+ and there are also qualitative differences in the response properties of these areas. KO has been first described as being especially sensitive to kinetic boundaries (Orban et al., 1995). Furthermore, when testing hMT/V5+, KO, and V3A with different coherencies of random-dot motion, Rees et al. (2000) could show that hMT/V5+ shows a linear relationship between motion coherence and activation, whereas the relationship for KO and V3A was U-shaped. Despite those differences, it is still possible that all those areas are necessary for the detection of motion directions in a random-dot pattern. Specific targeting of KO and V3A with neuronavigated TMS in future studies might reveal the functional contribution and relevant time windows for random-dot motion processing in those regions.

Our methodological approach enabled us to reveal and quantify the interindividual variance in the exact location of hMT/V5+ and the respective TMS target position on

the skull of the participants. Considering that shifting the TMS coil position only by a few millimeters can already lead to a complete loss of TMS effects (Beckers & Hömberg, 1992; d'Alfonso et al., 2002), our study clearly shows the benefits of a neuronavigated TMS procedure that is based on individual functional imaging data.

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References

Ahlfors, S.P., Simpson, G.V., Dale, A.M., Belliveau, J.W., Liu, A.K., Korvenoja, A., Virtanen, J., Huotilainen, M., Tootell, R.B.H., Aronen, H.J., & Ilmoniemi, R.J. (1999). Spatiotemporal activity of a cortical network for processing visual motion revealed by MEG and fMRI. *J. Neurophysiol., 82*, 2545-2555.

Albright, T.D., Desimone, R., & Gross, C.G. (1984). Columnar organization of directionally selective cells in visual area MT of the macaque. *J. Neurophysiol., 51*, 16-31.

Amassian, V.E., Cracco, R.Q., Maccabee, P.J., Cracco, J.B., Rudell, A.P., & Eberle, L. (1998). Transcranial magnetic stimulation in study of the visual pathway. *J. Clin. Neurophysiol., 15*, 288-304.

Anand, S., Olson, J.D., & Hotson, J.R. (1998). Tracing the timing of human analysis of motion and chromatic signals from occipital to temporo-parieto-occipital cortex: a transcranial magnetic stimulation study. *Vision Res., 38*, 2619-2627.

Antal, A., Kincses, T.Z., Nitsche, M.A., & Paulus, W. (2003). Manipulation of phosphene thresholds by transcranial direct current stimulation in man. *Exp. Brain Res., 150*, 375-378.

Antal, A., Nitsche, M.A., Kincses, T.Z., Lampe, C., & Paulus, W. (2004). No correlation between moving phosphene and motor thresholds: a transcranial magnetic stimulation study. *Neuroreport, 15*, 297-302.

Antal, A., Varga, E.T., Nitsche, M.A., Chadaide, Z., Paulus, W., Kovács, G., & Vidnyánszky, Z. (2004). Direct current stimulation over MT+/V5 modulates motion aftereffect in humans. *Neuroreport, 15*, 2491-2494.

Baker, C.L., Hess, R.F., & Zihl, J. (1991). Residual motion perception in a "motion-blind" patient, assessed with limited-lifetime random dot stimuli. *J. Neurosci., 11*, 454-461.

Beckers, G., & Hömberg, V. (1991). Impairment of visual perception and visual short term memory scanning by transcranial magnetic stimulation of occipital cortex. *Exp. Brain Res., 87*, 421-432.

Beckers, G., & Hömberg, V. (1992). Cerebral visual motion blindness: transitory akinetopsia induced by transcranial magnetic stimulation of human area V5. *Proc. R. Soc. Lond. B Biol. Sci., 249*, 173-178.

Beckers, G., & Zeki, S. (1995). The consequences of inactivating areas V1 and V5 on visual motion perception. *Brain, 118*, 49-60.

Boynton, G.M., Engel, S.A., Glover, G.H., & Heeger, D.J. (1996). Linear systems analysis of functional magnetic resonance imaging in human V1. *J. Neurosci., 16*, 4207-4221.

Campana, G., Cowey, A., & Walsh, V. (2002). Priming of motion direction and area V5/MT: a test of perceptual memory. *Cereb. Cortex, 12*, 663-669.

Cook, E.P., & Maunsell, J.H.R. (2002). Dynamics of neuronal responses in macaque MT and VIP during motion detection. *Nat. Neurosci., 5*, 985-994.

Corthout, E., Hallett, M., & Cowey, A. (2003). Interference with vision by TMS over the occipital pole: a fourth period. *Neuroreport, 14*, 651-655.

Cowey, A., & Walsh, V. (2001). Tickling the brain: studying visual sensation, perception and cognition by transcranial magnetic stimulation. *Prog. Brain Res., 134*, 411-425.

d'Alfonso, A.A.L., van Honk, J., Schutter, D.J.L.G., Caffé, A.R., Postma, A., & de Haan, E.H.F. (2002). Spatial and temporal characteristics of visual motion perception involving V5 visual cortex. *Neurol. Res., 24*, 266-270.

Diogo, A.C.M., Soares, J.G.M., Koulakov, A., Albright, T.D., & Gattass, R. (2003). Electrophysiological imaging of functional architecture in the cortical middle temporal visual area of Cebus apella monkey. *J. Neurosci., 23*, 3881-3898.

Dumoulin, S.O., Bittar, R.G., Kabani, N.J., Baker, C.L., Jr., Le Goualher, G., Pike, G.B., & Evans, A.C. (2000). A new anatomical landmark for reliable identification of human area V5/MT: a quantitative analysis of sulcal patterning. *Cereb. Cortex, 10*, 454-463.

Fernandez, E., Alfaro, A., Tormos, J.M., Climent, R., Martínez, M., Vilanova, H., Walsh, V., & Pascual-Leone, A. (2002). Mapping of the human visual cortex using image-guided transcranial magnetic stimulation. *Brain Res. Brain Res. Protoc., 10*, 115-124.

ffytche, D.H., Guy, C.N., & Zeki, S. (1995). The parallel visual motion inputs into areas V1 and V5 of human cerebral cortex. *Brain, 118*, 1375-1394.

Goebel, R., Khorram-Sefat, D., Muckli, L., Hacker, H., & Singer, W. (1998). The constructive nature of vision: direct evidence from functional magnetic resonance imaging studies of apparent motion and motion imagery. *Eur. J. Neurosci., 10*, 1563-1573.

Gulyas, B., Heywood, C.A., Popplewell, D.A., Roland, P.E., & Cowey, A. (1994). Visual form discrimination from color or motion cues: functional anatomy by positron emission tomography. *Proc. Natl. Acad. Sci. USA, 91*, 9965-9969.

Heeger, D.J., Boynton, G.M., Demb, J.B., Seidemann, E., & Newsome, W.T. (1999). Motion opponency in visual cortex. *J. Neurosci., 19*, 7162-7174.

Hotson, J.R., & Anand, S. (1999). The selectivity and timing of motion processing in human temporo-parieto-occipital and occipital cortex: a transcranial magnetic stimulation study. *Neuropsychologia, 37*, 169-179.

Hotson, J.R., Braun, D., Herzberg, W., & Boman, D. (1994). Transcranial magnetic stimulation of extrastriate cortex degrades human motion direction discrimination. *Vision Res., 34*, 2115-2123.

Howell, D.C. (2004). *Statistical Methods for Psychology* (5th ed.). Belmost, CA: Duxbury Press.

Huk, A.C., Dougherty, R.F., & Heeger, D.J. (2002). Retinotopy and functional subdivision of human areas MT and MST. *J. Neurosci., 22*, 7195-7205.

Hupé, J.M., James, A.C., Girard, P., Lomber, S.G., Payne, B.R., & Bullier, J. (2001). Feedback connections act on the early part of the responses in monkey visual cortex. *J. Neurophysiol., 85*, 134-145.

Muckli, L., Kriegeskorte, N., Lanfermann, H., Zanella, F.E., Singer, W., & Goebel, R. (2002). Apparent motion: event-related functional magnetic resonance imaging of perceptual switches and states. *J. Neurosci., 22*, RC219 (1-5).

Newsome, W.T., & Paré, E.B. (1988). A selective impairment of motion perception following lesions of the middle temporal visual area (MT). *J. Neurosci., 8*, 2201-2211.

Nowak, L.G., Munk, M.H., Nelson, J.I., James, A.C., & Bullier, J. (1995). Structural basis of cortical synchronization. I. Three types of interhemispheric coupling. *J Neurophysiol., 74*, 2379-2400.

Orban, G.A., Dupont, P., De Bruyn, B., Vogels, R., Vandenberghe, R., & Mortelmans, L. (1995). A motion area in human visual cortex. *Proc. Natl. Acad. Sci. USA, 92*, 993-997.

Orban, G.A., Van Essen, D., & Vanduffel, W. (2004). Comparative mapping of higher visual areas in monkeys and humans. *Trends Cogn. Sci., 8*, 315-324.

Pascual-Leone, A., & Walsh, V. (2001). Fast backprojections from the motion to the primary visual area necessary for visual awareness. *Science, 292*, 510-512.

Rees, G., Friston, K., & Koch, C. (2000). A direct quantitative relationship between the functional properties of human and macaque V5. *Nat. Neurosci., 3*, 716-723.

Sack, A.T., & Linden, D.E.J. (2003). Combining transcranial magnetic stimulation and functional imaging in cognitive brain research: possibilities and limitations. *Brain Res. Brain Res. Rev., 43*, 41-56.

Scherg, M., Linden, D.E.J., Muckli, L., Roth, R., Drüen, K., Ille, N., Linek, S., Zanella, F.E., Singer, W., & Goebel, R. (1999). Combining MEG with fMRI in studies of the human visual system. 129-132.

Seiffert, A.E., Somers, D.C., Dale, A.M., & Tootell, R.B.H. (2003). Functional MRI studies of human visual motion perception: texture, luminance, attention and after-effects. *Cereb. Cortex, 13*, 340-349.

Snowden, R.J., Treue, S., Erickson, R.G., & Andersen, R.A. (1991). The response of area MT and V1 neurons to transparent motion. *J. Neurosci., 11*, 2768-2785.

Stewart, L., Battelli, L., Walsh, V., & Cowey, A. (1999). Motion perception and perceptual learning studied by magnetic stimulation. *Electroencephalogr. Clin. Neurophysiol. Suppl., 51*, 334-350.

Théoret, H., Kobayashi, M., Ganis, G., Di Capua, P., & Pascual-Leone, A. (2002). Repetitive transcranial magnetic stimulation of human area MT/V5 disrupts perception and storage of the motion aftereffect. *Neuropsychologia, 40*, 2280-2287.

Tootell, R.B.H., Reppas, J.B., Dale, A.M., Look, R.B., Sereno, M.I., Malach, R., Brady, T.J., & Rosen, B.R. (1995). Visual motion aftereffect in human cortical area MT revealed by functional magnetic resonance imaging. *Nature, 375*, 139-141.

Tootell, R.B.H., Reppas, J.B., Kwong, K.K., Malach, R., Born, R.T., Brady, T.J., Rosen, B.R., & Belliveau, J.W. (1995). Functional analysis of human MT and related visual cortical areas using magnetic resonance imaging. *J. Neurosci., 15*, 3215-3230.

Vaina, L.M., & Cowey, A. (1996). Impairment of the perception of second order motion but not first order motion in a patient with unilateral focal brain damage. *Proc. R. Soc. Lond. B Biol. Sci., 263*, 1225-1232.

Van Essen, D.C., Maunsell, J.H.R., & Bixby, J.L. (1981). The middle temporal visual area in the macaque: myeloarchitecture, connections, functional properties and topographic organization. *J. Comp. Neurol., 199*, 293-326.

Walsh, V., & Cowey, A. (2000). Transcranial magnetic stimulation and cognitive neuroscience. *Nat. Rev. Neurosci., 1*, 73-79.

Walsh, V., Ellison, A., Ashbridge, E., & Cowey, A. (1999). The role of the parietal cortex in visual attention--hemispheric asymmetries and the effects of learning: a magnetic stimulation study. *Neuropsychologia, 37*, 245-251.

Walsh, V., Ellison, A., Battelli, L., & Cowey, A. (1998). Task-specific impairments and enhancements induced by magnetic stimulation of human visual area V5. *Proc. R. Soc. Lond. B Biol. Sci., 265*, 537-543.

Watson, J.D.G., Myers, R., Frackowiak, R.S.J., Hajnal, J.V., Woods, R.P., Mazziotta, J.C., Shipp, S., & Zeki, S. (1993). Area V5 of the human brain: evidence from a combined study using positron emission tomography and magnetic resonance imaging. *Cereb. Cortex, 3*, 79-94.

Zeki, S., Watson, J.D.G., Lueck, C.J., Friston, K.J., Kennard, C., & Frackowiak, R.S.J. (1991). A direct demonstration of functional specialization in human visual cortex. *J. Neurosci., 11*, 641-649.

Zeki, S.M. (1974). Functional organization of a visual area in the posterior bank of the superior temporal sulcus of the rhesus monkey. *J. Physiol., 236*, 549-573.

Zihl, J., von Cramon, D., & Mai, N. (1983). Selective disturbance of movement vision after bilateral brain damage. *Brain, 106*, 313-340.

CHAPTER 4

Imaging the Local and Remote Neural Effects Underlying Impaired Visuospatial Judgments During Parietal Magnetic Brain Stimulation

Based on manuscript:

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Abstract

Transcranial Magnetic brain Stimulation (TMS) is by now an established tool for inducing transient changes in neural activity, establishing causal relationships between local brain activity and specific behavioral or cognitive functions. These causal structure-function relationships are mostly indirectly inferred based on TMS-induced changes in behavior. The neural correlate by which TMS exerts its behavioral consequences, however, is only partly understood. Here, we applied TMS to the parietal cortices during functional magnetic resonance imaging (fMRI) of visuospatial judgments in order to concurrently observe its behavioral and neural effects in the active human brain. Our results show that right, but not left, parietal TMS (1) behaviorally impairs visuospatial judgment, (2) induces neural activity changes in a larger right-hemispheric network of fronto-parietal regions, and (3) shows significant correlations between TMS-induced behavioral impairments and neural activity changes in both the directly stimulated parietal and ipsilateral frontal brain regions. Our experiments indicate that concurrent functional imaging and magnetic brain stimulation during task execution might hold the potential to identify and visualize a network of brain areas that are functionally related to cognition and behavior. In the future, this would allow for causal structure-function inference across the entire brain.

Introduction

The execution of visuospatial tasks (Haxby, Grady, Horwitz, Ungerleider, Mishkin, Carson, Herscovitch, Schapiro, & Rapoport, 1991; Ungerleider & Haxby, 1994; Cohen, Kosslyn, Breiter, DiGirolamo, Thompson, Anderson, Brookheimer, Rosen, & Belliveau, 1996; Goebel, Linden, Lanfermann, Zanella, & Singer, 1998; Trojano, Grossi, Linden, Formisano, Hacker, Zanella, Goebel, & Di Salle, 2000; Sack, Sperling, Prvulovic, Formisano, Goebel, Di Salle, Dierks, & Linden, 2002b) as well as visuospatial imagery (Mellet, Tzourio, Crivello, Joliot, Denis, & Mazoyer, 1996; Trojano et al., 2000; Sack, Hubl, Prvulovic, Formisano, Jandl, Zanella, Maurer, Goebel, Dierks, & Linden, 2002a) leads to increased activations in the fronto-parietal cortices of the human brain, particularly the intraparietal sulcus region of both hemispheres (Formisano, Linden, Di Salle, Trojano, Esposito, Sack, Grossi, Zanella, & Goebel, 2002; Trojano, Grossi, Linden, Formisano, Goebel, Cirillo, Elefante, & Di Salle, 2002). Previous functional brain imaging results furthermore suggest a direct positive relationship between increased cognitive demand, as reflected in visuospatial task difficulty, and underlying neural activity, as reflected in increased neural responses in the parietal lobes (Tagaris, Kim, Strupp, Andersen, Ugurbil, & Georgopoulos, 1996; Carpenter, Just, Keller, Eddy, & Thulborn, 1999; Ng, Bullmore, de Zubicaray, Cooper, Suckling, & Williams, 2001; Vannini, Almkvist, Franck, Jonsson, Volpe, Kristoffersen, Wahlund, & Dierks, 2004).

However, although functional brain imaging provides evidence for transient local increases in neural activity during the execution of specific perceptual and cognitive processes, it does not permit inferences about causal structure-function relationships. Such inferences can only be made based on a controlled manipulation of brain activity whose impact on behavior or cognition can be quantified. The technique of transcranial magnetic stimulation (TMS) is by now a well established tool for inducing transient disruptions of neural activity ("virtual lesions") non-invasively in human volunteers. The strong magnetic fields that are generated over the brain for very brief periods systematically change the regional neural activity with replicable effects at the behavioral level (Hallett, 2000; Pascual-Leone, Walsh, & Rothwell, 2000; Walsh & Cowey, 2000; George, Nahas, Kozel, Li, Denslow, Yamanaka, Mishory, Foust, & Bohning, 2002). TMS can thus be regarded as a tool for the investigation of causal relationships between brain activity and behavior (Hallett, 2000; Pascual-Leone et al., 2000; Walsh & Cowey, 2000; Sack & Linden, 2003).

Accordingly, TMS has contributed to our understanding of the functional role of many superficial brain areas (i.e., those accessible to the manipulation). Concerning the topic of the present study, it has confirmed the relevance of parietal cortices in general visuospatial processing (Cohen et al., 1996; Topper, Mottaghy, Brugmann, Noth, & Huber, 1998; Rushworth, Johansen-Berg, Gobel, & Devlin, 2003; Vannini et al., 2004; Kim, Min, Ko, Park, Jang, & Lee, 2005; Koch, Oliveri, Torriero, & Caltagirone, 2005; Göbel, Calabria, Farne, & Rossetti, 2006), visuospatial attention (Hilgetag, Théoret, & Pascual-Leone, 2001; Stewart, Ellison, Walsh, & Cowey, 2001; Bestmann, Thilo, Sauner, Siebner, & Rothwell, 2002; Chambers, Payne, Stokes, & Mattingley, 2004; Hung, Driver, & Walsh, 2005), and visuomotor integration (Rushworth, Ellison, & Walsh, 2001). In previous studies our group showed that, although functional brain imaging reveals bilateral parietal activity during the execution of visuospatial tasks, only right parietal TMS significantly perturbs behavioral performance (Sack et al., 2002b; Sack, Camprodon, Pascual-Leone, & Goebel, 2005). The right-hemispheric dominance of parietal cortex for perceptual visuospatial proc-

essing (Sack *et al.*, 2002a), but also visuospatial imagery (Sack *et al.*, 2002b; Sack *et al.*, 2005), and visuospatial attention (Hilgetag et al., 2001; Müri, Bühler, Heinemann, Mosimann, Felblinger, Schlaepfer, & Hess, 2002; Sack et al., 2002b; Hung et al., 2005; Göbel et al., 2006), as determined by TMS, parallels the models of classical neuropsychology that are based on findings of hemispatial neglect after unilateral parietal damage.

This conclusion, however, is based on the implicit assumption that the TMS-induced behavioral impairments are indeed caused by TMS-induced local neural activity disruptions at the stimulation site of TMS. However, recent TMS studies indicate that focal TMS might not exclusively affect neural activity directly under the stimulation coil, but extends its neural consequences to remote and interconnected brain regions (Ferbert *et al.*, 1992; Bohning et al., 2000; Civardi *et al.*, 2001; Paus, 2002; Bestmann et al., 2004; Daskalakis *et al.*, 2004; Denslow et al., 2005; Pleger et al., 2006; Taylor et al., 2006). By simultaneously combining TMS and EEG during the execution of a cognitive task, Taylor et al. (2006) even revealed that these TMS-induced indirect neural effects might represent task-relevant functional activity changes in remote regions of the brain.

According to these recent findings, we cannot rule out at the moment that the previously revealed behavioral visuospatial impairments following right parietal TMS may not exclusively be caused by, or reflected in activity changes restricted to the site of stimulation, but be brought about by additionally induced neural activity changes in task-related remote brain regions.

This question, however, can only be answered by measuring task-related neural activity during TMS while assessing its behavioral and neural effects at the same time. Following the pioneering work of Paus (TMS&PET, 1997; see also Fox et al., 1997) and Bohning (TMS&fMRI, 1997), a couple of research groups have continued to establish the technical feasibility of applying TMS inside the scanner, directly measuring TMS-induced changes in brain activity across the entire brain (Bohning et al., 2000; Baudewig et al., 2001; Paus et al., 2002; Bestmann et al. 2004).

In the present study we aimed to use this novel methodological approach in order to investigate the task- and hemisphere-specific neural mechanisms of parietal TMS that might underlie the suggested right-hemispheric dominance during visuospatial judgments. We asked whether TMS-induced behavioral impairments are paralleled by brain activity changes solely at the site of stimulation, or whether they are accompanied by additional activity changes in remote brain regions that are part of a cortical network subserving visuospatial task processing.

In order to address this issue, we simultaneously combined fMRI and focal event-related TMS to the parietal lobes during the execution of two different tasks. Participants had to press a button whenever the hands of a visually presented analog clock formed a certain angle (ANGLE), or whenever the clock hands had a certain color (COLOR). While the ANGLE task required an explicit visuospatial judgment, the COLOR task served as a control condition in which mere color discriminations were required. We used fMRI to continuously measure changes in brain activity during the execution of both tasks. Tasks were presented in a classical block design during three different fMRI conditions: “task execution without TMS”, “task execution with simultaneous TMS”, “TMS during fixation”. During the condition “task execution with simultaneous TMS”, participants either received right or left parietal TMS to transiently disrupt neural processing, while simultaneously monitoring TMS-induced changes in brain activity and behavior.

Methods

Participants

Six healthy right-handed participants (mean age = 34.4; SD = 5.4; all male) with normal or corrected-to-normal vision without past neuropsychiatric history took part according to procedures approved by the local ethics committee. Prior to the experiment, informed consent was obtained from all participants.

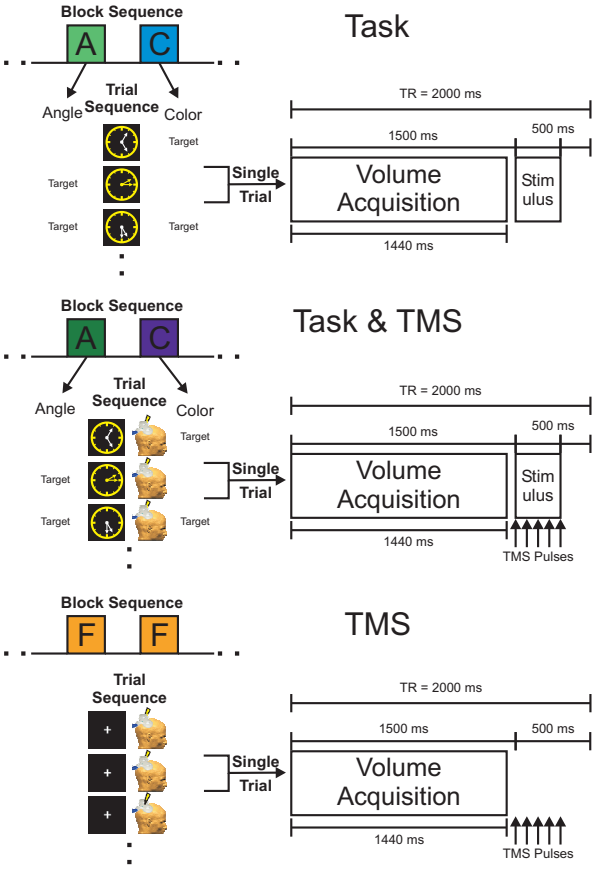

Figure 1. Stimuli, design and TMS protocol. Three experimental runs were conducted: TASK, TASK & TMS, and TMS. For TASK as well as TASK & TMS runs, blocks with the ANGLE task and COLOR task were alternated. In the TMS run, participants fixated continuously on a central fixation cross while TMS was applied at the same time as during the TASK & TMS run. For the two TMS runs (TASK & TMS and TMS only), TMS pulses were applied during temporal gaps (560 ms) between volume acquisitions to avoid interference with MR images.

Experimental setup

The study consisted of two separate fMRI experiments. In the first experiment, three fMRI runs (conditions) were conducted in a counterbalanced order: cognitive task executions without TMS (TASK), cognitive task executions with simultaneously applied TMS to the right parietal cortex (TASK & TMS), and TMS during central fixation (TMS). For the second fMRI experiment, the same participants were re-invited and tested again according to the same procedure as in the first fMRI experiment. However, unlike in the first experiment not the right but the left parietal cortex was stimu-

lated during the TASK & TMS condition. Hence, every participant completed two separate fMRI experiments (left versus right parietal TMS inside the MR scanner), each consisting of three different conditions (task executions without TMS, task executions with TMS, TMS during fixation).

Magnetic resonance imaging

MRI was performed at 3 Tesla (Siemens TRIO, Erlangen, Germany) using a standard transmit-receive head-coil. High resolution anatomical images were acquired using a short-echo time MP-RAGE sequence (TR/TE = 15/4 ms, flip angle 20º, 1 x 1 x 1 mm^3 resolution) covering the whole head. Functional images (16 oblique contiguous slices) were obtained using a T2*-weighted single-shot gradient-echo EPI sequence (TR/TE = 2000/36 ms, flip angle 70º, 96 x 128 matrix, frequency-selective fat suppression, 2 x 2 mm^2 resolution, 4 mm section thickness). Single volume acquisitions lasted 1440 ms (16 x 90ms); followed by a temporal gap of 560 ms. Participants wore earplugs and headphones for hearing protection while head motion was restricted using foam pads.

Transcranial magnetic stimulation

TMS was applied through a non-ferromagnetic figure-of-eight coil (70 mm outer wing diameter; two windings of ten turns each; inner winding diameter 53 mm; distance between outer coil surface and windings: 2-3 mm (variation due to manufacturing tolerance); coil inductance: 20 µH with a maximal current at 100% stimulator output of approximately 5 kA; initial rise time of biphasic pulse approximately 90 µs). The coil was additionally mechanically supported by an appropriately shaped 8 mm plastic former that was attached on the reverse side of the coil by high strength fiber tape (The Magstim Company, Whitland, Wales, UK). The coil was connected to a Magstim Rapid stimulator (The Magstim Company) outside the radiofrequency (RF) shielded cabin via an 8 m cable through an RF filter tube. TMS pulses were applied at an intensity of 100% maximum output and synchronized with the beginning of each new EPI volume acquisition by use of a 5 V TTL pulse. Note, however, that the effective output intensity in this setup was approximately 20% below a standard TMS setup, due to the resistive properties of the long connecting cable and slightly different coil characteristics. Interactions of magnetic stimulation and MR image acquisition were avoided by applying five TMS pulses in the 560 ms period subsequent to each volume acquisition at a frequency of ~13.3 Hz (i.e., at 1500, 1575, 1650, 1725, and 1800 ms). The remaining 200 ms period ensured that subsequent volume acquisition was unperturbed (Fig. 1).

TMS Localization

Since frameless stereotaxy is not applicable inside the MR scanner, we based the localization of TMS stimulation on the respective results of experimentally combined fMRI-rTMS studies (Sack *et al.*, 2002b; Sack *et al.*, 2005). In accordance with these results, stimulation was applied during both fMRI experiments, centering the TMS coil above the right or left parietal activation cluster with the coil producing an initial medio-lateral current orientation. To identify the exact position of the TMS coil also relative to the simultaneously measured structural and functional data sets and to thus allow for a post hoc identification of the stimulated position of the TMS coil and the underlying cortical region, vitamin capsules were attached to the plane of the TMS coil inside the MR scanner. The TMS coil centre was estimated by triangulation between the vitamin capsules, and the exact position and orientation of the coil inside the scanner was reconstructed by a projection perpendicular to the tangential plane

of the TMS coil centre. Hence, by visualizing the reconstruction of the exact coil position relative to the simultaneously acquired anatomical and functional images of each participant, we were able to post-hoc validate the cortical und functional region underlying the TMS coil (Fig. 2).

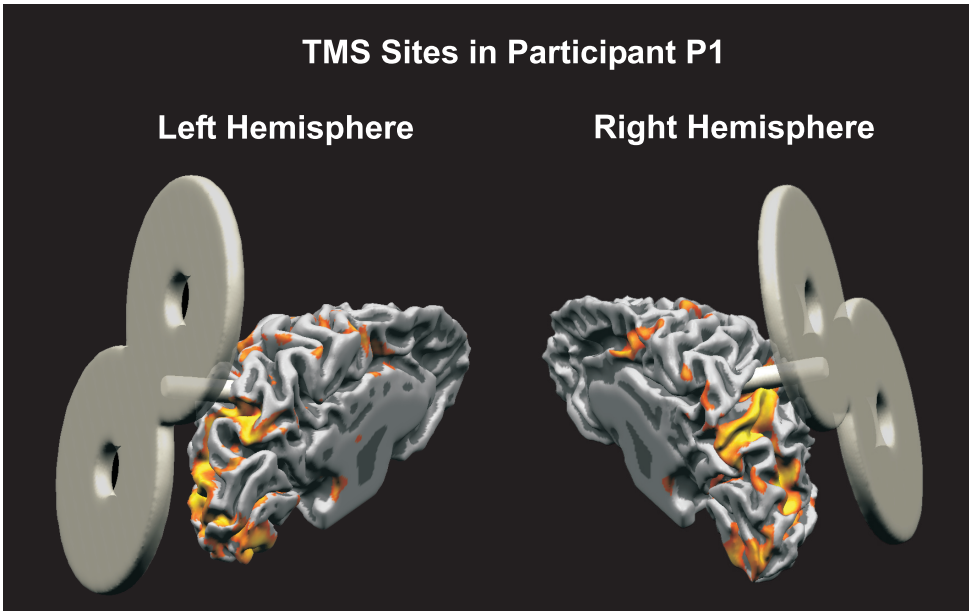

Figure 2. Localization of TMS coils in participant P1. Data-based reconstruction of the exact TMS coil positions relative to the neuronal activation during task execution of participant P1. The coil reconstruction is based on the signal of three vitamin E capsules that were attached to reference points on the coil during the measurements; those could be identified post-hoc in the anatomical scans. Areas that were significantly activated during the angle task are superimposed on the cortex reconstruction and color-coded in red to yellow (threshold, $p < 0.001$). The normal vector originating from the middle of the coil visualizes the estimated region of maximal stimulation effect below the TMS coil. Coil positioning for right and left parietal cortex was homologous (P4 and P3 electrode positions, respectively).

Cognitive tasks

The stimuli consisted of schematized analogue clocks with a yellow face and two white or yellow hands. Targets were defined as clocks with angles of 30° or 60° (angle discrimination task: ANGLE) or clocks with white hands (color task: COLOR). Participants were instructed to press a button as fast as possible using the index (target) or middle finger (non-target) of the right hand. Previous work has shown bilateral parietal activity during the execution of the ANGLE task (Sack *et al.*, 2002a; Vannini *et al.*, 2004), with significant behavioral impairments occurring only after a disruption of the right parietal cortex (Sack *et al.*, 2002a). Tasks were instructed visually prior to each block (ANGLE or COLOR) during which 10 stimuli were presented for 300 ms each at a rate of 2000 ms matching the TR of the MR imaging. Stimuli were presented 1500 ms after volume acquisition onset, coinciding with TMS pulses in the TMS condition. Each block was repeated 4 times (40 trials per run) and separated by 14 seconds resting periods resulting in a total time of 286 s for each run. Participants

were instructed to retain fixation of a red central fixation cross throughout the experiment.

Behavioral data analyses

The behavioral data were analyzed separately for both experiments with a two-way repeated measures ANOVA including the conditions TASK (ANGLE versus COLOR) and TMS (with versus without TMS) as within subject factors. Prior to the inference statistical testing, data was screened for statistical outliers according to the 2xIQR criterion. For the reaction time analyses only trials with correct responses were considered and averaged for the different experimental conditions. The reaction time data of the correct responses was further tested for normal distribution and variance homogeneity. These tests revealed the suitability of the reaction time data for parametric statistical testing.

FMRI data analyses

FMRI data pre-processing, analysis and visualization of the anatomical and functional images was performed using BrainVoyager QX (Brain Innovation, Maastricht, The Netherlands). Functional time series preprocessing included inter-scan slice time correction, linear trend removal, temporal high-pass filtering to remove low-frequency non-linear drifts of 5 or fewer cycles per time course, spatial smoothing with a Gaussian kernel (full width half maximum = 6mm), and 3D motion correction to correct for small head movements by aligning all volumes to the first volume via rigid body transformations. The data of one participant required translation and rotation motion correction parameters of more than 4 mm and was excluded from further analyses. Functional slices were coregistered to the anatomical volume and transformed into Talairach space.

The statistical analysis of the variance of the BOLD signal was based on the application of multiple regression analysis to time series of task-related functional activation (Friston, Holmes, Poline, Grasby, Williams, Frackowiak, & Turner, 1995). In the multi-subject fixed effects analysis, the general linear model of the experiment was computed from the z-normalized volume time courses. The multiple linear regression of the BOLD-response time course was calculated for each voxel using 10 predictors: ANGLE and COLOR task with and without TMS, as well as the TMS-only condition, for the right and for the left parietal stimulation site. The main effect of TASK was computed by contrasting the ANGLE task execution versus the COLOR task execution (regardless of TMS), and by color-coding the results according a blue-red scale; red indicating higher neural activity during the ANGLE compared to the COLOR task. The main effect of TMS was computed by contrasting task execution with TMS versus task execution without TMS (regardless of task), and by color-coding the results according a blue-red scale; blue indicating areas with significantly lower neural activity during task executions with TMS compared to those without TMS, and red indicating areas with significantly increased neural activity during task executions with TMS compared to task executions without TMS. Additionally, differences between neural activity changes during task execution with versus without TMS were also analyzed separately for both fMRI experiments (left versus right parietal TMS), and color-coded according to a blue-red scale, blue representing areas with significantly lower task-related activity during task execution with TMS (Fig. 3 and 4).

To determine statistical interaction effects, volume of interest (VOI) analyses were performed. VOI's were defined based on the computation of a multi-subject multiple regression analysis of the main effect of TASK using the GLM framework. This contrast analysis revealed the regional activations associated with both task executions.

The resulting fMRI activity map was thresholded at a t-value corresponding to q (FDR) < 005, and a spatial extent threshold of 100 mm^3. For each cluster within this fMRI activity map, a VOI analysis was conducted testing for possible first- and second-order interaction effects between TASK x TMS x SITE. The main effect of TASK contrast analysis thus served as an independent localizer for the subsequent VOI analyses in order to ensure a statistically independent selection criterion for defining the VOI's.

All statistical contrast maps were projected on the inflated representation of a template brain (Montreal Neurological Institute). The obtained p values were corrected for multiple comparisons using the False Discovery Rate approach (Genovese, Lazar, & Nichols, 2002).

The application of TMS pulses during fMRI measurements, as realized in this study, represents a technically and methodologically demanding enterprise limiting the number of measured participants. As a consequence, the fMRI group data was analyzed based on a fixed effects analysis. The described result patterns were consistent across participants.

Results

FMRI results of task execution without TMS

The analysis of fMRI signal changes during task execution compared to baseline revealed that both ANGLE and COLOR task execution resulted in an increase of neural activity in striate and extrastriate visual cortex, bilateral inferior and superior parietal lobule (IPL, SPL), bilateral inferior and middle frontal gyrus (IFG, MFG), bilateral frontal eye fields (FEF), bilateral supplementary motor area (SMA), bilateral fusifrom gyrus, and bilateral primary motor cortex (PMC) (Sack et al., 2002a).

A direct statistical contrast analysis between ANGLE versus COLOR task execution regardless of TMS was computed in order to directly compare fMRI signal differences between both tasks. This main effect of TASK revealed a significantly stronger neural activity during the ANGLE compared to the COLOR task in the left and right occipital lobe, the left and right IPL, the left and right SPL, and the left and right MFG.

Behavioral effects of right parietal TMS

The statistical analyses of the reaction times during right parietal TMS were based on a two-way repeated measures ANOVA with the conditions TASK (ANGLE versus COLOR) and TMS (with versus without TMS) as within-subject factors. The analyses revealed a significant main effect of TASK ($F = 23$; $p = 0.05$), no main effect of TMS ($F = 4.3$; $p = 0.93$), and a significant interaction between TASK and TMS ($F = 10.1$; $p = 0.025$). Post-hoc simple contrast analyses revealed that only the reaction times in the ANGLE task were significantly increased during right parietal TMS ($t = 3.136$, $p = 0.026$), while no significant impairment was found for the COLOR task ($t = 1.258$, $p = 0.265$). Note that although the main effect of TASK indicates that the ANGLE task required significantly longer reaction times compared to the COLOR task, the significant TASK x TMS interaction statistically ensures that the revealed task-dependent behavioral effects of right parietal TMS were not confounded by difficulty differences between both tasks. Similar to the reaction time data, we also analyzed the accuracy differences between the different conditions. Although the analyses failed to reach statistical significance (no main or interaction effects), the results are descriptively in accordance with the task-dependent effect of right parietal TMS. While the average error rate in the ANGLE task increased from 2.7 false responses without TMS to 4.2

false responses during right parietal TMS, the accuracy level for the COLOR task remained unaffected (2.8 false responses without TMS versus 2.2 false responses during TMS).

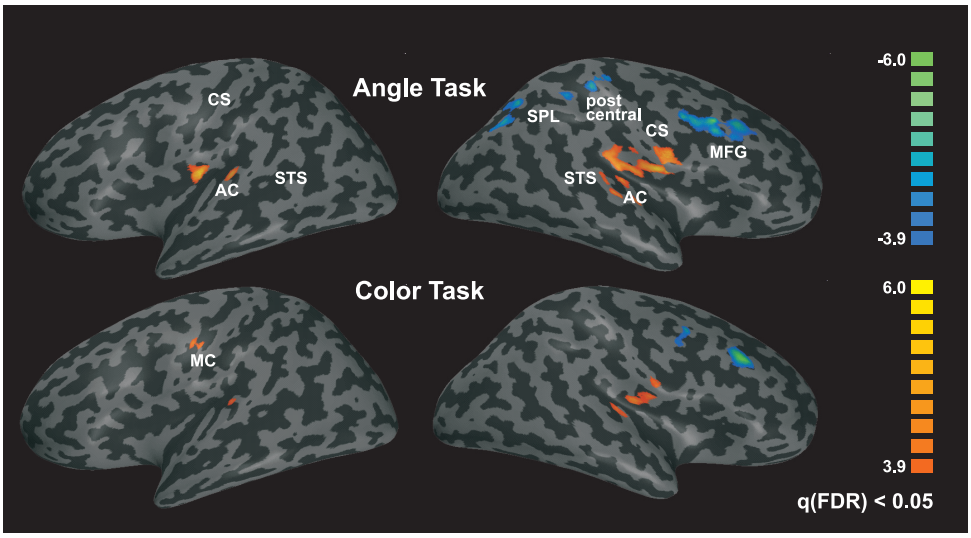

Figure 3. Changes in task-related brain activity during right parietal TMS. Task execution with versus without right parietal TMS, separately for ANGLE and COLOR task. Results are projected onto the inflated hemispheres of the MNI template brain. Blue indicates areas with a significantly reduced neural activity during task execution with TMS, and red areas with a significantly increased neural activity induced by TMS. SPL = Superior Parietal Lob-ule, MFG = Middle Frontal Gyrus, AC = Auditory Cortex, MC = Motor Cortex, OC = Occipital Cortex, STS = Superior Temporal Sulcus, CS = Central Sulcus.

Behavioral effects of left parietal TMS

The statistical analyses of the behavioral data during left parietal TMS revealed a completely different result pattern. In contrast to the revealed task-dependent behavioral impairments during right parietal TMS, a TMS-induced disruption of the left parietal cortex resulted in no behavioral performance changes in either task. The analyses of the reaction times revealed a main effect of TASK ($F = 18$; $p = 0.013$), no main effect of TMS ($F = 0.1$; $p = 0.828$) and no interaction between TASK x TMS ($F = 0.6$; $p = 0.477$). The reaction times during left parietal TMS were almost identical to the reaction times without TMS and did not differ significantly from baseline, as revealed by post-hoc simple contrast analyses (ANGLE: - 7.2 ms, $t = 0.467$, $p = 0.665$; COLOR: + 17.5 ms; $t = 0.497$, $p = 0,645$). The accuracy analyses revealed no significant main or interaction effects, nor did the descriptive tendency indicate any difference between the different conditions. Similar to the reaction time data, error rates during left parietal TMS were almost identical to the error rates without TMS.

These task- and hemisphere-specific behavioral effects of parietal TMS inside the MR scanner replicate our previous findings outside the MR scanner. In these earlier offline TMS studies we already demonstrated, based on a much larger sample size, that right parietal TMS significantly impaired performance in the angle, but not the

color discrimination task, while left parietal TMS led to no behavioral impairment in either task (Sack et al., 2002b; Sack et al., 2002a).

FMRI effects of right parietal TMS

When comparing BOLD signal changes during task execution with versus without right parietal TMS, we found significant TMS-induced BOLD signal reductions in the right SPL (stimulated), the right postcentral gyrus, and the right MFG during the ANGLE task, while no such effect was observed for the COLOR task (Fig. 3). This difference in TMS-induced reduction of neural activity between both tasks was particu-

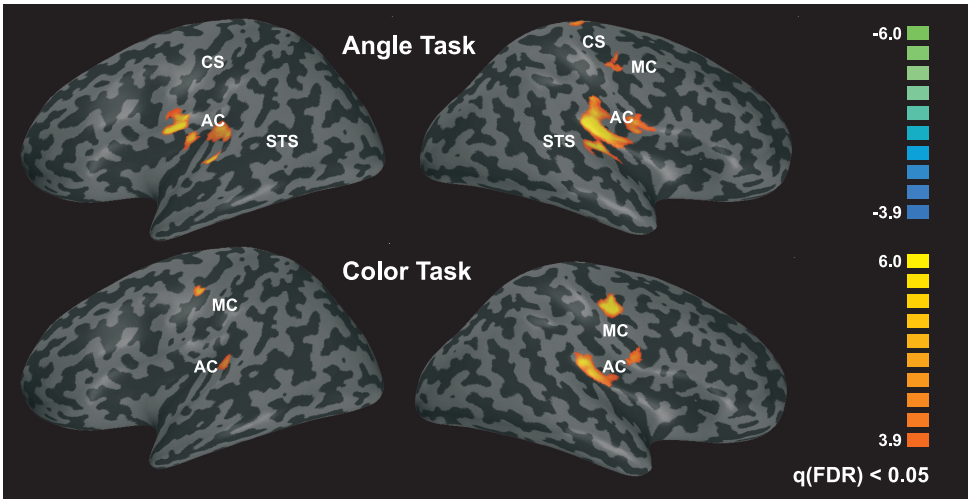

Figure 4. Changes in task-related brain activity during left parietal TMS. Task execution with versus without left parietal TMS, separately for ANGLE and COLOR task. Results are superimposed on the inflated hemispheres of the MNI template brain. Blue indicates areas with a significantly reduced neural activity during task execution with TMS, and red areas with a significantly increased neural activity induced by TMS. SPL = Superior Parietal Lob-ule, AC = Auditory Cortex, MC = Motor Cortex, OC = Occipital Cortex, STS = Supe-rior Temporal Sulcus, CS = Central Sulcus.

larly pronounced in the right SPL and MFG (Fig. 3). Accordingly, a two-way ANOVA of neural activity revealed a significant interaction between TASK (ANGLE versus COLOR) and TMS (with versus without) only in the superior parietal lobe ($F = 2.614$, $p < 0.05$) and MFG ($F = 2.523$, $p < 0.05$) of the right hemisphere. Moreover, a significant correlation between the degree of activity reduction and the strength of the behavioral impairment was only found for the ANGLE task and only in the right SPL ($r = 0.94$, $p < 0.05$) and right MFG ($r = 0.87$; $p < 0.05$).

All other activated regions, including areas in the occipito-temporal and parieto-occipital cortex, did not show any task-specific differences. While the superior occipital gyrus showed similar neural activation levels during all experimental conditions, and thus independent of TASK and TMS (Fig. 3), the left and right SMA, FEF and left SPL showed a TMS-induced reduction that was of equal strength for both tasks. The left and right auditory cortices also showed no task-specific difference in their TMS-induced increase of neural activity caused by the discharge noise of the TMS coil (Siebner, Peller, Willoch, Auer, Bartenstein, Drzezga, Schwaiger, & Conrad, 1999).

Increased activation during right parietal TMS was also observed in the parietal operculum of both hemispheres and the inferior part of the left central sulcus. While the former probably reflects the activation of bilateral secondary somatosensory cortex due to peripheral nerve stimulation, the latter is likely caused by contralateral peripheral muscle stimulation at the stimulation site of TMS.

FMRI effects of left parietal TMS

In contrast to the right parietal TMS effects, the left parietal stimulation induced a different pattern of fMRI results. When comparing BOLD signal changes during task execution with left parietal TMS to those without, we only found significant TMS-induced BOLD signal increases in bilateral auditory and predominantly right motor areas (Fig. 4). The left and right auditory cortices showed no task-specific difference in their TMS-induced increase of neural activity caused by the discharge noise of the TMS coil (Fig. 4). The increased motor cortex activity predominantly on the right side likely reflects the contralateral peripheral muscle stimulation at the stimulation site of TMS. The bilateral occipital cortex and the left and right SPL showed similar neural activation levels during all experimental conditions, and this independent of TASK and TMS (Fig. 4). Importantly, none of the brain areas showed an interaction between TASK (ANGLE versus COLOR) and TMS (with versus without), nor did any of the areas show a significant correlation between the TMS-induced changes in brain activity and changes in behavioral performances.

Volume-of-interest interaction effects

Volume-of-interest (VOI) analyses were computed in order to directly compare the neural effects between both stimulation sites and to test for possible second-order interactions between the different experimental conditions. These analyses revealed a significant interaction between TASK (ANGLE versus COLOR) x TMS (with versus without) x SITE (left parietal versus right parietal) in right SPL ($t = 2.0$, $p = 0.05$), right postcentral gyrus ($t = 1.9$; $p = 0.05$), and right MFG ($t = 2.5$, $p = 0.01$). These analyses further support the notion that within this right-hemispheric fronto-parietal network, the neural effects of TMS are task-dependent and significantly different between both stimulation sites. The asymmetry of behavioral effects between left versus right parietal virtual lesions is thus mirrored by an asymmetry of the respective neural consequences.

Discussion

In the present study we directly compared the physiological and behavioral consequences of virtual brain lesions, as evoked by magnetic brain stimulation, during visuospatial processing. Using the novel combination of concurrent TMS and fMRI, we show that TMS to right parietal cortex selectively impairs visuospatial judgments but not an appropriate control task that used identical visual stimuli. Critically, we were able to visualize the impact of this disruption on neural activity and show that a decrease in task performance is mirrored by a corresponding decrease of cortical activity not only at the site of stimulation but also in remote and interconnected frontal brain regions of the same hemisphere.

Both visual tasks, angle and color discrimination, resulted in increased neural activity in parietal and frontal regions of both hemispheres. However, only the magnetic manipulation of right parietal activity significantly impaired the behavioral performance in the ANGLE but not in the COLOR task. In contrast, TMS-induced disruptions

of left parietal activity led to no impairments in the behavioral performance of either task. TMS of the right parietal cortex not only resulted in a relative decrease of activity within the vicinity of the stimulated right SPL, but also in several frontal regions within the same hemisphere. This TMS-induced reduction of neural activity within a right-hemispheric fronto-parietal network was significantly stronger for the visuospatial judgment task (ANGLE) than for the color discrimination task (COLOR). Hence, the same task that showed the significant behavioral impairment also showed stronger neural effects of right parietal magnetic stimulation. Moreover, only the right SPL and MFG showed a significant correlation between the degree of reduced neural activity and the strength of the behavioral impairment induced by TMS. In addition, we also identified areas that showed a similar pattern of a TMS-induced reduction of neural activity for both tasks. These included the SMA, FEF and regions of the left parietal lobule and might represent brain regions linked to more general cognitive or visual abilities that are equally called upon by both tasks. As no significant behavioral impairment was observed in the COLOR task, one might speculate that these activity decreases were not directly linked to the observed behavioral impairment.

In contrast, left parietal TMS led to no task-specific activity decreases. The absence of behavioral effects following left parietal TMS is thus mirrored by an absence of TMS-induced reductions of neural activity. Accordingly, no interaction between TMS and TASK condition, and no correlations between TMS-induced activity changes and task performance were found during left parietal TMS. We could thus directly relate the asymmetry of behavioral consequences following left versus right parietal lesions to an asymmetry of the respective neural effects in the brain.

The absence of significant activity changes at the site of stimulation in left parietal cortex might seem puzzling at first, considering that the parietal lobes of both hemispheres showed activity increases during execution of both tasks. However, a direct comparison of neural activity during the ANGLE versus COLOR task execution revealed significantly more activity in right parietal cortex during the ANGLE task. This stronger right parietal activity during the visuospatial judgment task may have facilitated the effect of TMS. This would be analogous to the observation that TMS to primary motor cortex induced stronger peripheral muscle movements and facilitated motor-evoked potentials when applied during voluntary contraction as opposed to a relaxed muscle state (Tunstill, Wynn-Davies, Nowicky, McGregor, & Davey, 2001).

There are several possible explanations for our results. The most straightforward explanation would be that the local neural effects of TMS propagate to interconnected brain regions. Several studies show that this is indeed the case (Ferbert, Priori, Rothwell, Day, Colebatch, & Marsden, 1992; Civardi, Cantello, Asselman, & Rothwell, 2001; Daskalakis, Paradiso, Christensen, Fitzgerald, Gunraj, & Chen, 2004). For example, recent neuroimaging studies showed activity changes correlated to TMS in broad functional networks within the brain (Chouinard, Van Der Werf, Leonard, & Paus, 2003; Speer, Willis, Herscovitch, Daube-Witherspoon, Shelton, Benson, Post, & Wassermann, 2003b; Speer, Willis, Herscovitch, Daube-Witherspoon, Shelton, Benson, Post, & Wassermann, 2003a; Li, Nahas, Kozel, Anderson, Bohning, & George, 2004), including basal ganglia (Strafella, Paus, Barrett, & Dagher, 2001) and the thalamus (Bestmann, Baudewig, Siebner, Rothwell, & Frahm, 2004; Denslow, Lomarev, George, & Bohning, 2005). Moreover, neural network models indicate that the effects of TMS propagate to both directly and indirectly connected remote sites (Husain, Nandipati, Braun, Cohen, Tagamets, & Horwitz, 2002). In the present study, these remote activity changes were functionally coupled with activity at the site of stimulation during the execution of the task in question, and activity changes both at the site of stimulation *and* remote brain regions may have caused

the behavioral perturbation we observed. However, whether remote activity changes are brought about by ortho- or antidromic activation (Amassian, Maccabee, Cracco, Cracco, Somasundaram, Rothwell, Eberle, Henry, & Rudell, 1994; Fox, Ingham, George, Mayberg, Ingham, Roby, Martin, & Jerabek, 1997; Lisanby, Luber, Perera, & Sackeim, 2000) of long-range projection neurons or local intracortical activity, which then propagate mono- or polysynaptically into respective target regions is presently unclear.

Alternatively, the observed remote activity changes may be a consequence of the perturbed behavior. It is conceivable that TMS mainly exerts its behavioral effect by disrupting activity at the site of stimulation, but activity in additional remote brain regions reacts to this disruption, exhibiting activity changes which are highly correlated to the site of stimulation. We also cannot exclude the possibility that the remote activity changes simply co-varied with local and presumably causally relevant activity changes, but did not contribute to the behavioral perturbation.

From these considerations it becomes clear that the exact physiological underpinnings of TMS-induced activity decreases have not yet been fully clarified. Although the exact mechanisms of these activity changes, and their causal relevance to the observed behavioral perturbation remain to be elucidated, our study exemplifies how concurrent TMS and fMRI can be used to chart brain activity changes to a transient TMS-induced behavioral perturbation non-invasively and with high spatial precision. In particular, we have confirmed the involvement of right parietal cortex in visuospatial processing and shown that a TMS-induced impairment of this behavior is not only paralleled by activity changes at the site of disruption, but also by ipsilateral activity changes in lateral frontal cortex.

Conclusion

We propose that the simultaneous combination of TMS with fMRI during task execution provides an important opportunity to assess the direct and remote neural underpinnings of virtual brain lesions. In this sense, concurrent TMS and functional imaging should be regarded as a complementary approach to behavioral TMS studies, helping to refine the causal topography of structure-function relationships across the entire brain. The challenge for future studies will be to disclose the functional relevance of the TMS-induced direct and remote neural effects, aiming to distinguish brain areas that cause the behavioral changes from those that simply represent covariates or consequences of the induced changes in cognition and behavior.

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References

Amassian, V.E., Maccabee, P.J., Cracco, R.Q., Cracco, J.B., Somasundaram, M., Rothwell, J.C., Eberle, L., Henry, K., & Rudell, A.P. (1994). The polarity of the induced electric field influences magnetic coil inhibition of human visual cortex: implications for the site of excitation. *Electroencephalogr. Clin. Neurophysiol., 93*, 21-26.

Bestmann, S., Baudewig, J., Siebner, H.R., Rothwell, J.C., & Frahm, J. (2004). Functional MRI of the immediate impact of transcranial magnetic stimulation on cortical and subcortical motor circuits. *Eur. J. Neurosci., 19*, 1950-1962.

Bestmann, S., Thilo, K.V., Sauner, D., Siebner, H.R., & Rothwell, J.C. (2002). Parietal magnetic stimulation delays visuomotor mental rotation at increased processing demands. *Neuroimage, 17*, 1512-1520.

Carpenter, P.A., Just, M.A., Keller, T.A., Eddy, W., & Thulborn, K. (1999). Graded functional activation in the visuospatial system with the amount of task demand. *J. Cogn. Neurosci., 11*, 9-24.

Chambers, C.D., Payne, J.M., Stokes, M.G., & Mattingley, J.B. (2004). Fast and slow parietal pathways mediate spatial attention. *Nat. Neurosci., 7*, 217-218.

Chouinard, P.A., Van Der Werf, Y.D., Leonard, G., & Paus, T. (2003). Modulating neural networks with transcranial magnetic stimulation applied over the dorsal premotor and primary motor cortices. *J. Neurophysiol., 90*, 1071-1083.

Civardi, C., Cantello, R., Asselman, P., & Rothwell, J.C. (2001). Transcranial magnetic stimulation can be used to test connections to primary motor areas from frontal and medial cortex in humans. *Neuroimage, 14*, 1444-1453.

Cohen, M.S., Kosslyn, S.M., Breiter, H.C., DiGirolamo, G.J., Thompson, W.L., Anderson, A.K., Brookheimer, S.Y., Rosen, B.R., & Belliveau, J.W. (1996). Changes in cortical activity during mental rotation. A mapping study using functional MRI. *Brain, 119*, 89-100.

Daskalakis, Z.J., Paradiso, G.O., Christensen, B.K., Fitzgerald, P.B., Gunraj, C., & Chen, R. (2004). Exploring the connectivity between the cerebellum and motor cortex in humans. *J. Physiol., 557*, 689-700.

Denslow, S., Lomarev, M., George, M.S., & Bohning, D.E. (2005). Cortical and subcortical brain effects of transcranial magnetic stimulation (TMS)-induced movement: an interleaved TMS/functional magnetic resonance imaging study. *Biol. Psychiatry, 57*, 752-760.

Ferbert, A., Priori, A., Rothwell, J.C., Day, B.L., Colebatch, J.G., & Marsden, C.D. (1992). Interhemispheric inhibition of the human motor cortex. *J. Physiol., 453*, 525-546.

Formisano, E., Linden, D.E.J., Di Salle, F., Trojano, L., Esposito, F., Sack, A.T., Grossi, D., Zanella, F.E., & Goebel, R. (2002). Tracking the mind's image in the brain I: time-resolved fMRI during visuospatial mental imagery. *Neuron, 35*, 185-194.

Fox, P., Ingham, R., George, M.S., Mayberg, H., Ingham, J., Roby, J., Martin, C., & Jerabek, P. (1997). Imaging human intra-cerebral connectivity by PET during TMS. *Neuroreport, 8*, 2787-2791.

Friston, K.J., Holmes, A.P., Poline, J.B., Grasby, P.J., Williams, S.C., Frackowiak, R.S., & Turner, R. (1995). Analysis of fMRI time-series revisited. *Neuroimage, 2*, 45-53.

Genovese, C.R., Lazar, N.A., & Nichols, T. (2002). Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *NeuroImage, 15*, 870-878.

George, M.S., Nahas, Z., Kozel, F.A., Li, X., Denslow, S., Yamanaka, K., Mishory, A., Foust, M.J., & Bohning, D.E. (2002). Mechanisms and state of the art of transcranial magnetic stimulation. *J. ECT, 18*, 170-181.

Göbel, S.M., Calabria, M., Farne, A., & Rossetti, Y. (2006). Parietal rTMS distorts the mental number line: Simulating 'spatial' neglect in healthy subjects. *Neuropsychologia, 44*, 860-868.

Goebel, R., Linden, D.E., Lanfermann, H., Zanella, F.E., & Singer, W. (1998). Functional imaging of mirror and inverse reading reveals separate coactivated networks for oculomotion and spatial transformations. *Neuroreport, 9*, 713-719.

Hallett, M. (2000). Transcranial magnetic stimulation and the human brain. *Nature, 406*, 147-150.

Haxby, J.V., Grady, C.L., Horwitz, B., Ungerleider, L.G., Mishkin, M., Carson, R.E., Herscovitch, P., Schapiro, M.B., & Rapoport, S.I. (1991). Dissociation of object and spatial visual processing pathways in human extrastriate cortex. *Proc. Natl. Acad. Sci. USA, 88*, 1621-1625.

Hilgetag, C.C., Théoret, H., & Pascual-Leone, A. (2001). Enhanced visual spatial attention ipsilateral to rTMS-induced 'virtual lesions' of human parietal cortex. *Nat. Neurosci., 4*, 953-957.

Hung, J., Driver, J., & Walsh, V. (2005). Visual selection and posterior parietal cortex: effects of repetitive transcranial magnetic stimulation on partial report analyzed by Bundesen's theory of visual attention. *J. Neurosci., 25*, 9602-9612.

Husain, F.T., Nandipati, G., Braun, A.R., Cohen, L.G., Tagamets, M.A., & Horwitz, B. (2002). Simulating transcranial magnetic stimulation during PET with a large-scale neural network model of the prefrontal cortex and the visual system. *Neuroimage, 15*, 58-73.

Kim, Y.H., Min, S.J., Ko, M.H., Park, J.W., Jang, S.H., & Lee, P.K. (2005). Facilitating visuospatial attention for the contralateral hemifield by repetitive TMS on the posterior parietal cortex. *Neurosci. Lett., 382*, 280-285.

Koch, G., Oliveri, M., Torriero, S., & Caltagirone, C. (2005). Modulation of excitatory and inhibitory circuits for visual awareness in the human right parietal cortex. *Exp. Brain Res., 160*, 510-516.

Li, X., Nahas, Z., Kozel, F.A., Anderson, B., Bohning, D.E., & George, M.S. (2004). Acute left prefrontal transcranial magnetic stimulation in depressed patients is associated with immediately increased activity in prefrontal cortical as well as subcortical regions. *Biol. Psychiatry, 55*, 882-890.

Lisanby, S.H., Luber, B., Perera, T., & Sackeim, H.A. (2000). Transcranial magnetic stimulation: applications in basic neuroscience and neuropsychopharmacology. *Int. J. Neuropsychopharmacol., 3*, 259-273.

Mellet, E., Tzourio, N., Crivello, F., Joliot, M., Denis, M., & Mazoyer, B. (1996). Functional anatomy of spatial mental imagery generated from verbal instructions. *J. Neurosci., 16*, 6504-6512.

Müri, R.M., Bühler, R., Heinemann, D., Mosimann, U.P., Felblinger, J., Schlaepfer, T.E., & Hess, C.W. (2002). Hemispheric asymmetry in visuospatial attention assessed with transcranial magnetic stimulation. *Exp. Brain Res., 143*, 426-430.

Ng, V.W., Bullmore, E.T., de Zubicaray, G.I., Cooper, A., Suckling, J., & Williams, S.C. (2001). Identifying rate-limiting nodes in large-scale cortical networks for visuospatial processing: an illustration using fMRI. *J. Cogn. Neurosci., 13*, 537-545.

Pascual-Leone, A., Walsh, V., & Rothwell, J. (2000). Transcranial magnetic stimulation in cognitive neuroscience--virtual lesion, chronometry, and functional connectivity. *Curr. Opin. Neurobiol., 10*, 232-237.

Rushworth, M.F., Ellison, A., & Walsh, V. (2001). Complementary localization and lateralization of orienting and motor attention. *Nat. Neurosci., 4*, 656-661.

Rushworth, M.F., Johansen-Berg, H., Gobel, S.M., & Devlin, J.T. (2003). The left parietal and premotor cortices: motor attention and selection. *Neuroimage (Suppl. 1), 20*, S89-100.

Sack, A.T., Camprodon, J.A., Pascual-Leone, A., & Goebel, R. (2005). The dynamics of interhemispheric compensatory processes in mental imagery. *Science, 308*, 702-704.

Sack, A.T., Hubl, D., Prvulovic, D., Formisano, E., Jandl, M., Zanella, F.E., Maurer, K., Goebel, R., Dierks, T., & Linden, D.E.J. (2002a). The experimental combination of rTMS and fMRI reveals the functional relevance of parietal cortex for visuospatial functions. *Brain Res. Cogn. Brain Res., 13*, 85-93.

Sack, A.T., & Linden, D.E.J. (2003). Combining transcranial magnetic stimulation and functional imaging in cognitive brain research: possibilities and limitations. *Brain Res. Brain Res. Rev., 43*, 41-56.

Sack, A.T., Sperling, J.M., Prvulovic, D., Formisano, E., Goebel, R., Di Salle, F., Dierks, T., & Linden, D.E.J. (2002b). Tracking the mind's image in the brain II: transcranial magnetic stimulation reveals parietal asymmetry in visuospatial imagery. *Neuron, 35*, 195-204.

Siebner, H.R., Peller, M., Willoch, F., Auer, C., Bartenstein, P., Drzezga, A., Schwaiger, M., & Conrad, B. (1999). Imaging functional activation of the auditory cortex during focal repetitive transcranial magnetic stimulation of the primary motor cortex in normal subjects. *Neurosci. Lett., 270*, 37-40.

Speer, A.M., Willis, M.W., Herscovitch, P., Daube-Witherspoon, M., Shelton, J.R., Benson, B.E., Post, R.M., & Wassermann, E.M. (2003a). Intensity-dependent regional cerebral blood flow during 1-Hz repetitive transcranial magnetic stimulation (rTMS) in healthy volunteers studied with H215O positron emission tomography: I. Effects of primary motor cortex rTMS. *Biol. Psychiatry, 54*, 818-825.

Speer, A.M., Willis, M.W., Herscovitch, P., Daube-Witherspoon, M., Shelton, J.R., Benson, B.E., Post, R.M., & Wassermann, E.M. (2003b). Intensity-dependent regional cerebral blood flow during 1-Hz repetitive transcranial magnetic stimulation (rTMS) in healthy volunteers studied with H215O positron emission tomography: II. Effects of prefrontal cortex rTMS. *Biol. Psychiatry, 54*, 826-832.

Stewart, L., Ellison, A., Walsh, V., & Cowey, A. (2001). The role of transcranial magnetic stimulation (TMS) in studies of vision, attention and cognition. *Acta Psychol., 107*, 275-291.

Strafella, A.P., Paus, T., Barrett, J., & Dagher, A. (2001). Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. *J. Neurosci., 21*, RC157.

Tagaris, G.A., Kim, S.G., Strupp, J.P., Andersen, P., Ugurbil, K., & Georgopoulos, A.P. (1996). Quantitative relations between parietal activation and performance in mental rotation. *Neuroreport, 7*, 773-776.

Topper, R., Mottaghy, F.M., Brugmann, M., Noth, J., & Huber, W. (1998). Facilitation of picture naming by focal transcranial magnetic stimulation of Wernicke's area. *Exp. Brain Res., 121*, 371-378.

Trojano, L., Grossi, D., Linden, D.E.J., Formisano, E., Goebel, R., Cirillo, S., Elefante, R., & Di Salle, F. (2002). Coordinate and categorical judgements in spatial imagery. An fMRI study. *Neuropsychologia, 40*, 1666-1674.

Trojano, L., Grossi, D., Linden, D.E.J., Formisano, E., Hacker, H., Zanella, F.E., Goebel, R., & Di Salle, F. (2000). Matching two imagined clocks: the functional anatomy of spatial analysis in the absence of visual stimulation. *Cereb. Cortex, 10*, 473-481.

Tunstill, S.A., Wynn-Davies, A.C., Nowicky, A.V., McGregor, A.H., & Davey, N.J. (2001). Corticospinal facilitation studied during voluntary contraction of human abdominal muscles. *Exp. Physiol., 86*, 131-136.

Ungerleider, L.G., & Haxby, J.V. (1994). 'What' and 'where' in the human brain. *Curr. Opin. Neurobiol., 4*, 157-165.

Vannini, P., Almkvist, O., Franck, A., Jonsson, T., Volpe, U., Kristoffersen, W.M., Wahlund, L.O., & Dierks, T. (2004). Task demand modulations of visuospatial processing measured with functional magnetic resonance imaging. *Neuroimage, 21*, 58-68.

Walsh, V., & Cowey, A. (2000). Transcranial magnetic stimulation and cognitive neuroscience. *Nat. Rev. Neurosci., 1*, 73-79.

CHAPTER 5

Deciding What to See: The Role of Intention and Attention in the Perception of Apparent Motion

Based on manuscript:

Kohler, A., Haddad, L., Singer, W., & Muckli, L. (2006). Deciding what to see: The role of intention and attention in the perception of apparent motion. *Submitted*.

Abstract

Apparent motion is an illusory perception of movement that can be induced by alternating presentations of static objects. Already in Wertheimer's early investigation of the phenomenon [Wertheimer, M. (1912). Experimentelle Studien über das Sehen von Bewegung. *Z. Psychol., 61*, 161-265], he mentions that voluntary attention can influence the way in which an ambiguous apparent-motion display is perceived. But until now, few studies have investigated how strong the modulation of apparent motion through attention can be under different stimulus and task conditions. We used bistable motion quartets of two different sizes, where the perception of vertical and horizontal motion is equally likely. Eleven observers participated in two experiments. In Experiment 1, participants were instructed to either (a) hold the current movement direction as long as possible, (b) passively view the stimulus, or (c) switch the movement directions as quickly as possible. With the respective instructions, observers could almost double phase durations in (a) and more than halve durations in (c) relative to the passive condition. This modulation effect was stronger for the large quartets. In Experiment 2, observers' attention was diverted from the stimulus by a detection task at fixation while they still had to report their conscious perception. This manipulation prolonged dominance durations for 70-80% on average independent of quartet size. The experiments reveal a high susceptibility of ambiguous apparent motion to attentional modulation. We discuss how feature- and space-based attention mechanisms might contribute to those effects.

Introduction

Apparent motion is an illusory perception of movement that is induced by a sequence of static displays (Roget, 1825). The phenomenon has been extensively studied in early 20th century psychology (DeSilva, 1928; Duncker, 1929; Kenkel, 1913; Korte, 1915; Neuhaus, 1930; Schiller, 1933) and was a central paradigm for the initiation of the Gestalt movement (Sekuler, 1996; Steinman, Pizlo, & Pizlo, 2000; Wertheimer, 1912). Already Wertheimer (1912), in his classic paper, reports the fact that an observer's focus of attention can significantly bias the perception of an ambiguous apparent-motion display. According to his theory, spatial attention boosts processing at the attended location and thereby leads to faster processing times for the attended alternative, making it more likely to be perceived.

Since this time, there have been only few studies addressing the issue of attentional modulation of apparent motion. Ramachandran and Anstis (1983; 1985) mention that in their experiments with bistable apparent-motion displays, observers were able to voluntarily control the perceived motion direction. They do not describe any quantitative measures for the amount of modulation but report that the influence breaks down when the apparent motion speed is increased (stimulus onset asynchronies below 350 ms). Suzuki and Peterson (2000) investigated another type of bistable apparent motion and found a multiplicative effect of intentional effort on perception: The more the stimulus itself was biased towards a certain interpretation, the more effective was the voluntary influence.

The purpose of our study was to further investigate the extent of modulation by intention and attention for bistable apparent motion. We used the so-called 'motion quartet' (Hoeth, 1968; Neuhaus, 1930; Ramachandran & Anstis, 1983; Schiller, 1933), in which two pairs of dots at opposing corners of a virtual rectangle are presented in sequence so that either horizontal or vertical apparent motion can be perceived. The stimuli were presented in two different sizes in both experiments to see how modulation strength is affected by quartet size. In Experiment 1, observers were instructed to speed up and slow down percept changes in the motion quartet. The resulting percept durations were compared to a passive condition. In Experiment 2, spatial attention was diverted from the motion quartet with an attention-demanding detection task while participants still reported their conscious perception of the quartet. In this way, we were able to see how attentional focus affects the dynamics of bistable apparent motion.

Methods

Observers

Eleven members of the Frankfurt cognitive-neuroscience community (three authors, 8 naïves; age, 21-35) participated in experiments 1 and 2. All observers had normal or corrected-to-normal vision and were right-handed.

Stimuli and Apparatus

Experiment 1. Stimuli were generated with a custom-made program based on the Microsoft DirectX library and presented on a cathode-ray-tube monitor (Samsung SynchMaster). The distance between the participants' eyes and the monitor was 47 cm and the screen size 36.5 × 27.4 cm (field of view, 42.4° × 32.5° visual angle). The

participant's position was fixed with a chin and forehead rest. The stimulus consisted of four circles (diameter, 1.7°) arranged as a virtual rectangle (Fig. 1). At any given time, only two dots at diagonally opposite corners were presented. A fixation cross (size, 0.3° × 0.3°) was always displayed in the middle of the screen. Stimuli had a Michelson contrast of 100%. There were two versions of the motion quartet: (a) large, with a fixed horizontal distance between dots of 11° and a variable, observer-dependent vertical distance between 11° and 20.1°; (b) small, with a fixed horizontal distance between dots of 3.3° and a variable, observer-dependent vertical distance between 3.3° and 6.3°. Dots were presented for 150 ms with an interstimulus interval of 100 ms (2 Hz presentation frequency).

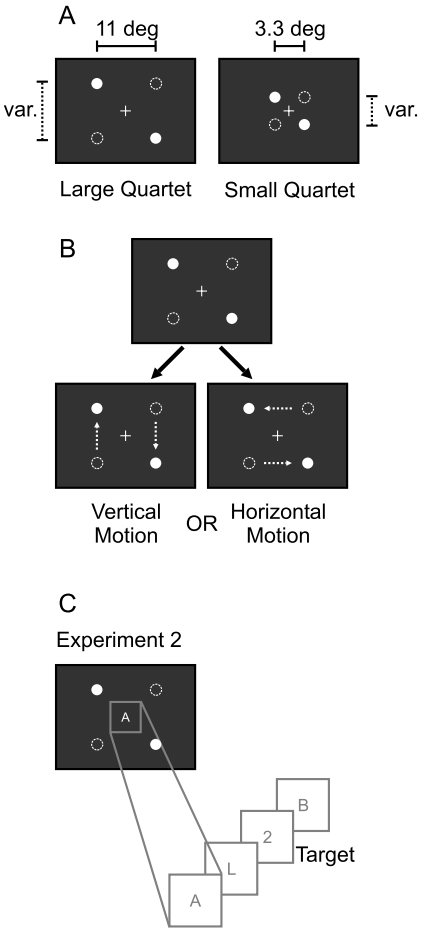

Figure 1. Stimuli for Experiments 1 and 2. (A) For both experiments, large and small quartets were used. The horizontal distance was fixed and the vertical distance was adjusted for individual participants according to a preceding threshold measurement. The diagonally opposing pairs of dots (filled and dashed) were presented in alternation, leading to a percept of either vertical or horizontal motion (B). During prolonged viewing, the perceived motion direction oscillated between the two possible interpretations. (C) In Experiment 2, participants had to fixate a character stream in the middle of the screen instead of a fixation cross. During the Task condition, they had to detect and report the numerical characters among the sequence of letters.

Experiment 2. The motion-quartet stimuli used in experiment 2 were identical to experiment 1 (large and small quartets). Instead of a fixation cross, participants looked at a character stream at the center of the screen (Fig. 1C). The stream consisted of alphanumeric characters (fixed height, 0.3°); the presentation frequency

of the characters was 2 Hz and numeric characters appeared with a probability of p = .125.

Procedure

Threshold Measurements. The optimal ratio between vertical and horizontal distance (aspect ratio) that leads to equal durations of vertical and horizontal motion perception can vary widely between observers. To get a balanced stimulus for every single participant, we used a 'Method of Limits' procedure to adjust the aspect ratio before the experiments began. The procedure was started by presenting a motion quartet with a very low aspect ratio (fixed horizontal distance, 6.6°; starting value for vertical distance, 4.4°) leading to unambiguous perception of vertical motion. The vertical distance was then ramped up and down in steps of 0.6° per 500 ms. Observers had to press a key when their perception switched between horizontal and vertical motion, which also reversed the direction of the step changes. Eleven percept reversals were recorded, the first value was discarded, and the average value of the remaining ten reversals was taken as the optimal aspect ratio for all following measurements. Participants were run in a test trial to familiarize them with the procedure before the actual threshold measurement was acquired.

Experiment 1. In the first experiment, participants received instructions to control the perceived direction in the motion-quartet stimulus. For every trial, they had one of three possible instructions: (i) "Try to alternate between vertical and horizontal perception as often as possible." (ii) "Passively observe the motion quartet." (iii) "At any time, try to hold the currently perceived motion direction. If the percept changes, try to hold the new perceived direction." Observers were instructed to report their perception (vertical/horizontal) by holding down one of two keys. If they didn't see any motion (motion breakdown), they were told to press no key. They were reminded to report their actual perception as veridically as possible, even when they had instructions to influence their perception. Most importantly, participants were instructed to keep steady fixation at any time. The combination of instructions (Switch/Passive/Hold) and stimulus size (large/small) resulted in six different conditions. Two trials each lasting two minutes were administered for each condition (twelve trials overall). The trials were presented in two blocks (random sequence) with a one-minute break in between. Before the start of the actual experiment, observers were familiarized with the instructions and the stimuli in two test trials.

Experiment 2. In the second experiment, the stimulus display had a stream of alphanumeric characters instead of a fixation cross. Besides reporting the perceived motion direction of the motion quartet as in experiment 1, observers had two possible additional instructions: (i) "Press a key when a numerical character is presented at fixation." (ii) "Press the key at random intervals, on average every four seconds." The first task was used to divert participants' attention from the motion quartet. The second instruction was employed as a control for any effects button presses might have on perceptual stability. In both conditions, participants were instructed to keep steady fixation on the alphanumerical character stream and report the changes in perceived motion direction as accurately as possible. Observers were familiarized with the attention-control task in a test trial. Two task types (attention task/passive viewing) and two stimulus sizes combine to four different trial types. Two trials were run per condition (eight trials overall). The trial sequence was randomly intermixed.

Data Analysis

The durations of the individual percept phases (horizontal or vertical motion) were used as dependent variable. Phases with no motion perception were rare and discarded from the analysis. Also, the last phase of each trial was discarded, since the trial duration was fixed (2 min) and the last phase had therefore an arbitrary value. For each observer, phase durations were normalized to (divided by) the average phase duration in the passive condition, separately for small and large quartets. The distributions of phase durations were fitted with a gamma distribution (maximum-likelihood estimate) using Matlab 7.0.4.365 (The MathWorks, Inc., Natick, MA, United States of America). Statistical comparisons between conditions were performed with a repeated-measures multivariate analysis of variance (MANOVA) using the software package SPSS 12.0.1 (SPSS, Inc., Chicago, IL, United States of America). To assess the correlations between subsequent phase durations, we performed lag-1 autocorrelations on phase-duration sequences, separately for observers and conditions. We then calculated a weighted average of the correlation coefficients across participants and tested for significance with an F statistic.

Results

Threshold Measurements

Before the experimental runs, we determined the optimal aspect ratio between vertical and horizontal distance for each participant with a ramping procedure. The

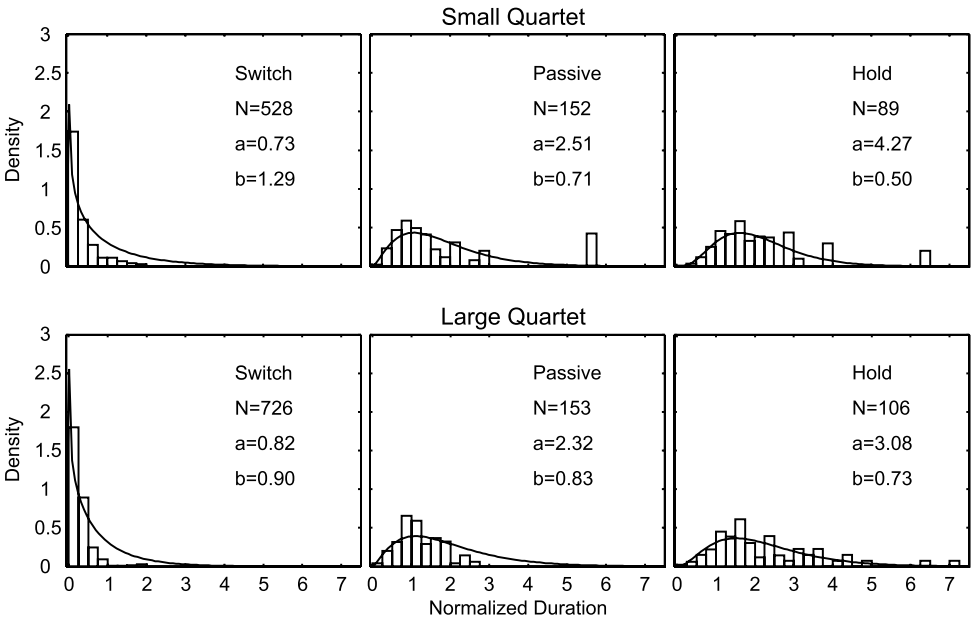

Figure 2. Distributions of phase durations for Experiment 1. Histograms and best-fitting gamma distributions for all conditions and quartet sizes. For each participant, phase durations were normalized to the mean value in the passive condition, separately for large and small quartets. The parameters of the gamma distributions were calculated using maximum-likelihood estimates.

optimal value for bistable apparent motion (50 % vertical and 50 % horizontal percept) can vary widely between observers (Selmes, Fulham, Finlay, Chorlton, & Manning, 1997; Sterzer & Kleinschmidt, 2005). In our sample the average aspect ratio was 1.41, ranging from 1.0 to 1.88 (Table 1). The threshold procedure was validated by calculating the ratio for the sum of vertical and horizontal phase durations as well as the ratio for the average vertical and horizontal phase durations. For both measures, the group values were around 1.0 in Experiment 1 (sum of durations, 1.01; average durations, 0.98), and around 0.9 in Experiment 2 (sum of durations, 0.90; average durations, 0.89).

Table 1. Threshold values for all participants (N=11).

	Pre	*Exp. 1*		*Exp. 2*	
Participant	Aspect Ratio	Ratio for Sum of Durations	Ratio for Phase Durations	Ratio for Sum of Durations	Ratio for Phase Durations
P1	1.28	1.00	1.03	0.93	0.53
P2	1.58	0.95	0.86	0.62	0.75
P3	1.48	0.91	0.90	0.41	0.69
P4	1.18	0.76	0.84	0.16	0.79
P5	1.57	0.84	0.87	1.10	1.02
P6	1.47	1.54	1.29	0.43	0.38
P7	1.17	1.14	1.11	1.16	0.87
P8	1.35	0.67	0.79	1.06	1.23
P9	1.88	1.18	1.14	1.13	0.77
P10	1.00	1.15	1.07	1.04	1.20
P11	1.52	0.97	0.87	1.85	1.51
Average	1.41	1.01	0.98	0.90	0.89

Notes. *Pre* – Aspect ratio (vertical length of motion quartet divided by horizontal length) as determined in the threshold measurements. *Exp. 1* and *Exp. 2* – Ratios between vertical and horizontal values for sum of durations and phase durations. For optimal bistability, the ratio values should be 1.

Experiment 1

In Experiment 1, we tested the ability of our participants to voluntarily influence the perceived direction of movement in the ambiguous motion quartet. They were instructed to either (i) switch the percept as often as possible, (ii) passively view the percept, or (iii) hold the current percept as long as possible. Typically, the dynamics of perceptual alternations in multistable displays, such as binocular rivalry or the Necker cube, is characterized by gamma-distributed phase durations (but see Brascamp, van Ee, Pestman, & van den Berg, 2005) and low correlations between subsequent perceptual episodes (Lehky, 1988; Leopold & Logothetis, 1999; Muckli, Kriegeskorte, Lanfermann, Zanella, Singer, & Goebel, 2002). In order to compare the perceptual dynamics of our stimulus to other paradigms and to assess the possible influence of the different conditions on the dynamics, we analyzed the distributions and autocorrelation functions in the different conditions. In all conditions, the distribution of phase durations could be well approximated by a gamma distribution (Fig. 2). From the displays in Figure 2 it is clear that the shape of the distributions in the Switch conditions (small and large quartet) is clearly more exponential-like (distribution parameter $a < 1$), since there is a high percentage of phase durations near the lower bound of 0. In addition to the distribution of phase durations, we also analyzed the lag-1 autocorrelation of phase sequences. We calculated the correlation values in single participants (separately for conditions) and then derived a weighted group mean of the correlation coefficients. For the Passive and Hold conditions,

correlation coefficients were below .10 and non-significant ($p > .30$), similar to other multistable stimuli. In contrast, for both quartet sizes correlations between subsequent periods in the Switch condition were positive and significant: small quartet – $r = .30$, $F(1, 526) = 51.241$, $p < .001$; large quartet – $r = .25$, $F(1, 724) = 48.758$, $p < .001$.

For the small quartet, the average absolute phase duration for the Passive condition was 21.4 s (range, 8.3 s to 56.3 s). The value for the Hold condition was 37.6 s (range, 15.4 s to 119.0 s) and 8.9 s (range, 1.7 to 20.4 s) for the Switch condition. The respective values for the large quartet were Passive – 16.9 s (range, 7.3 s to 38.0 s); Hold – 33.1 s (range, 12.8 s to 98 s); Switch – 5.1 s (range, 1.9 s to 10.7 s). This indicates that participants were able to substantially increase and reduce phase durations. As can be seen from Figure 3, this effect was present in every single observer. The group analysis was performed with a repeated-measures MANOVA on the normalized phase durations with the factors 'instruction' (Hold, Passive, Switch) and 'size' (small and large quartet). There was a significant effect for 'instruction' (Pillai's trace = .921, $F(2, 9) = 52{,}441$, $p < .001$) as well as for the

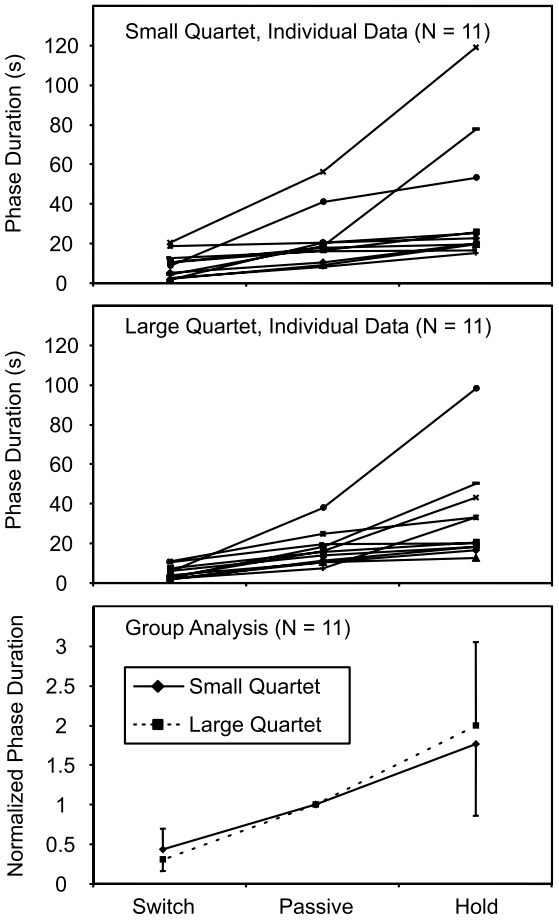

Figure 3. Individual and group results for Experiment 1. Results for individual participants separated by quartet size (upper two panels). Group results across eleven observers (lower panel). In the group analysis, phase durations were normalized to the mean value in the passive condition for each participant. Error bars denote standard deviations across participants.

interaction ‘instruction × size’ (Pillai’s trace = .505, F(2,9) = 4.590, p = .042), but no effect for ‘size’ (p = .775). From Figure 3 (lower panel) it becomes clear that the interaction effect was due to a more effective control with large quartets in the Hold as well as the Switch condition. With large quartets, phase durations in the Hold condition were exactly doubled relative to the Passive condition, the increase with small quartets was only 0.77 (difference = 0.23). Also in the Switch condition, normalized phase durations were reduced by 0.69 with large quartets and only by 0.56 for small quartets (difference = 0.13).

Experiment 2

In Experiment 2, we wanted to probe the influence of spatial attention on the dynamics of percept changes. In psychophysical (Chaudhuri, 1990) and imaging studies (Murray & Wojciulik, 2004), it could be demonstrated that attention enhances adaptation of motion sensors. We wanted to test (a) whether the same holds true for bistable stimuli, (b) whether it is specific to the perceived direction, and (c) how strong the modulatory effect would be. To this end, we manipulated the focus of attention by a demanding detection task in the center of the screen (Task condition). Observers had to monitor a character stream and detect the numerical characters among letters (Chaudhuri, 1990). At the same time, they had to report the direction of

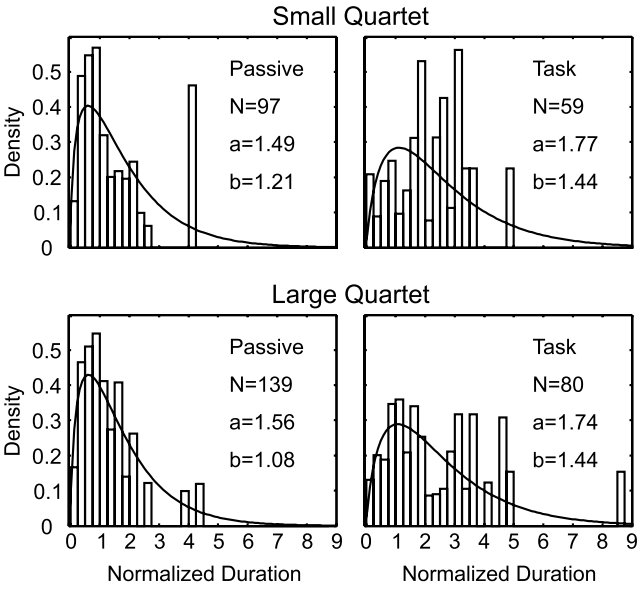

Figure 4. Distributions of phase durations for Experiment 2. Histograms and best-fitting gamma distributions for all conditions and quartet sizes. For each participant, phase durations were normalized to the mean value in the passive condition, separately for large and small quartets. The parameters of the gamma distributions were calculated using maximum-likelihood estimates.

motion in the motion quartet. In the Passive condition, observers had to maintain fixation on the same character stream but did not perform the detection task. To mimic the possible influence of button presses and for a minimal dual-task demand, participants had to randomly press the button used in the Task condition.

Data analysis was similar to Experiment 1. First, we assessed the dynamics of perceptual changes for the different conditions. Again all distributions could be fit with a gamma function, but the distributions in the Task condition deviated from the typical right-skewed pattern (Fig. 4). For both quartet sizes, the peaks were broader and the

gradual drop-off to the right was missing. In terms of the autocorrelation functions, no significant lag-1 correlations between phases were found in any condition ($p > .10$). The absolute mean phase durations for the Task condition were 47.9 s (range, 20.3 s to 117.5 s; small quartet) and 35.5 s (range, 14.4 s to 119.0 s; large quartet). In the Passive condition, the respective values were 30.4 s (range, 11.2 s to 63.0 s) and 20.9 s (range, 10.6 s to 52.3 s). For Experiment 2, the average phase durations in the Passive condition were longer than for Experiment 1, which might be due to the button-press task and the character stream at fixation. The normalized durations were analyzed using a repeated-measures MANOVA with factors 'instruction' (Task and Passive) and 'size' (small and large quartet, Fig. 5). The only significant effect was found for 'instruction' (Pillai's trace = .504, $F(1, 10) = 10.161$, $p = .01$). The effects for 'size' and the interaction were non-significant ($p > .50$). This was true despite the fact that also in Experiment 2, the modulation strength was greater for the large than the small quartets (1.82 vs. 1.69 normalized phase durations). This might be due to the higher inter-individual variance of the results in Experiment 2.

Discussion

In our experiments, we investigated the effect of voluntary control (Experiment 1) and attentional focus (Experiment 2) on the perceived direction of movement in the ambiguous motion quartet. We also tested the influence of distance/eccentricity of stimuli on the modulation magnitude. Observers' ability to influence their movement percept was substantial. With the corresponding instructions, they could almost double (Hold) and more than halve (Switch) the phase durations for horizontal/vertical motion. This effect was stronger by about 20% (average for enhancement and suppression) for the large compared to the small quartets. A comparable modulation effect – at least in magnitude – was found in Experiment 2, where in one condition observers had to perform an attention-demanding center task while tracking perceived movement of the motion quartet. Through this manipulation, percept durations were increased by 70-80%. The effect was again stronger for the large quartet by 13%, but the difference was not significant across participants.

The dynamics of perceptual alternations for both experiments were comparable to other multistable phenomena. Most of the distributions were well fit by a gamma distribution and in almost all cases correlation coefficients were small and non-significant. There were three notable exceptions: (a) In the Switch condition of Experiment 1, the shape of the gamma distribution was more exponential (distribution parameter $a < 1$) than the typical right-skewed Gaussian-type shape. This was due to the fact that participants were well able to substantially reduce percept durations by more than 50%, bringing them near the lower bound of 0 s. An exponential-like shape would imply that a rising edge on the left is missing, as is also suggested by Figure 2. But when we examined the distribution shape with smaller bin sizes, a rising edge on the left became apparent. Still, the width of the distribution was very small relative to the peak, which explains the low values of the gamma distributions' parameter *a*. (b) Also in the Switch condition of Experiment 1, the correlations between subsequent phase durations were highly significant with a medium effect size (small quartet, $r = .30$; large quartet, $r = .25$). This cannot be due to differences between participants since we calculated the correlation coefficients individually and then performed a weighted average. During the experiments, observers reported the Switch condition to be the most demanding one of all conditions because it required a lot of effort to constantly try to change the movement

direction against the prepotent tendency of the percept to stay constant immediately after a switch. It is possible that observers' vigilance and effort drifted or oscillated slowly over the duration of a two-minute trial, which would lead to a positive correlation between subsequent percept durations. Alternatively, participants became more effective in manipulating their conscious perception and therefore showed a drift across trial duration. (c) Percept durations for multistable phenomena are supposed to be gamma-distributed (Leopold & Logothetis, 1999; Levelt, 1967). In most conditions, our data sets showed a good fit to the gamma distribution, although we cannot rule out that other functions provide an even better fit, as suggested by Brascamp and colleagues (2005). Only the distributions for the Task condition (small and large quartet) in Experiment 2 showed a clear deviation from the gamma pattern. The peaks were broader (small quartet) or even bimodal (large quartet) and there was no apparent skew on the right flank of the distributions. It is possible that the phase durations across different observers were too heterogeneous to provide a good fit. The individual data in Figure 4 show that some observers even showed a reduction in phase durations relative to the Passive condition. Since phase durations were normalized to the Passive condition in individual participants, heterogeneity of effects could lead to a reduced fit of the gamma distribution across observers. Because of the low number of phases in single participants, we were unable to assess distribution fits for single participants.

In a previous study, Ramachandran and Anstis (1985) reported that their observers were able to intentionally manipulate the movement direction in a quartet display, but only when the stimulus-onset asynchrony (SOA) was above 350 ms. The SOA in our experiments was 250 ms, but, as reported, our participants showed a very strong control over their conscious perception. The reason for this difference might be that the distance between dots (more than 3° visual angle) and also the dot size (1.7°) in our stimulus was much larger than in the study of Ramachandran and Anstis. The distance between dots in their displays was 40 min of arc and the dot size 3 min of arc; these values are near the parameter range reported for short-range apparent-motion displays (Braddick, 1980). Therefore, it is possible that there are qualitative differences between stimuli with different distances and dot sizes. We explicitly tested the scaling of voluntary control with distance between dots and found a significant enhancement of control (by about 20%) with larger distance. Although the modulation strength for the small quartet was still very high, it is possible that voluntary control breaks down when the quartet size is very small. In addition, voluntary control could be dependent on the SOA, so that for smaller distances, voluntary control is only possible with longer SOA values (Ramachandran & Anstis, 1985).

A recurrent concern in the investigation of multistable displays is the systematic influence of eye movements. This issue has been extensively studied for binocular rivalry (Blake, Fox, & McIntyre, 1971; Lack, 1971), where it has been shown that percept alternations do not exclusively depend on eye movements. But it is still possible that eye movements play a significant role, especially when participants receive explicit instructions to control their conscious perception. In a recent series of experiments, van Dam and van Ee (2006) meticulously investigated the relationship between perceptual alternations and eye movements in different perceptual-rivalry as well as binocular-rivalry paradigms. They found that there was a positive correlation between percept changes and saccades in binocular rivalry but not for perceptual rivalry (Necker cube and slant rivalry). Notably, this pattern did not change when observers had explicit instructions to influence their percept, suggesting that voluntary control is not exerted through saccades. Although we cannot rule out

completely the occurrence of differential patterns of eye movements in our experiments, it is unlikely that they could account for the substantial modulation strength we found, given the results described above (van Dam & van Ee, 2005; 2006).

There has been a recent resurgence of interest in the amount of voluntary control and the influence of spatial attention on rivaling stimuli (Chong, Tadin, & Blake, 2005; Chong & Blake, 2006; Meng & Tong, 2004; van Ee, 2005; van Ee, van Dam, & Brouwer, 2005), especially binocular rivalry but also other types of perceptual rivalry. Meng and Tong (2004) compared the amount of control for different types of binocular rivalry and the Necker cube. They could show that voluntary selection of one of two possible percepts is well possible with the Necker cube but not with binocular rivalry. The modulation strength was about 40% for the Necker cube and only 10% for binocular rivalry. In addition, they tested non-selective control of the bistable stimuli, i.e., a non-specific increase or decrease in alternation rate. In this case, for both stimulus types they found a strong influence on alternation rates,

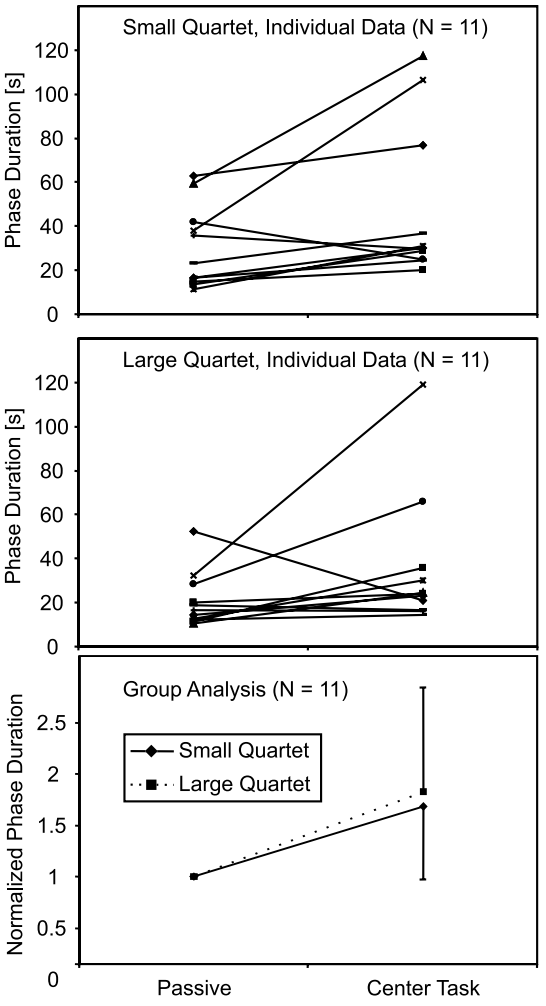

Figure 5. Individual and group results for Experiment 2. Results for individual participants separated by quartet size (upper two panels). Group results across eleven observers (lower panel). In the group analysis, phase durations were normalized to the mean value in the passive condition for each participant. Error bars denote standard deviations across participants.

especially for the speed-up of percept switches; the effect for the Necker cube was comparable to the results we found in Experiment 1, the effect for binocular rivalry was weaker. A major difference to our experiment was that participants in Meng and Tong's study could slow down the alternation rate of the Necker cube and binocular rivalry only by about 30 %, whereas our participants could almost double phase durations in the Hold condition of Experiment 1. Similar results to those of Meng and Tong were reported by van Ee and colleagues (van Ee, 2005; van Ee et al., 2005). In addition to the Necker cube and binocular rivalry, they also investigated the recently developed 'slant rivalry' paradigm (van Ee, van Dam, & Erkelens, 2002), where the interpretation of depth structure is ambiguously determined either by perspective cues or disparity. Interestingly, slant rivalry showed the highest susceptibility to control and also had the longest dominance durations during passive viewing (about 6 s). Our stimulus has even longer natural dominance durations (about 20-30 s) and could easily be controlled voluntarily. It is possible that longer natural dominance durations facilitate the exertion of voluntary control, although this factor cannot exhaustively determine the degree of modulation. First, the Necker cube has about the same natural dominance duration as binocular rivalry but is much more prone to selective influence. Second, in our experiments the large-quartet stimulus could be controlled more easily than the small quartet, although the natural dominance duration was smaller for the large quartet by 5-10 s.

In a series of experiments, Chong and colleagues could show that, under specific conditions, the selective effects of attention on binocular rivalry can be substantial (Chong & Blake, 2006; Chong et al., 2005). They found an increase of dominance durations of up to 80% when participants were engaged in an attention-demanding task on one of the rivaling targets (Chong et al., 2005). This modulation could be mimicked by increasing the contrast for the stimulus of interest during its dominance phases, suggesting that attention does in fact enhance perceived contrast, as has been suggested by other studies (Carrasco, Ling, & Read, 2004). They argue that the task is a necessary prerequisite for the effect of attention and explains the differences to the other studies described above, in which participants were only instructed to manipulate their conscious perception. What implications do the data of Chong and colleagues have for our results? Is it possible that the voluntary control of the motion quartet found in Experiment 1 and the attentional modulation of Experiment 2 rely on the same mechanism of contrast enhancement through attention? This is unlikely given the following arguments: (a) Observers could enhance as well as reduce dominance durations in Experiment 1, whereas in Chong et al.'s study attention only enhanced the duration of the attended percept. (b) The mechanism would have to act selectively on a specific motion direction. If one assumes that only the contrast of the inducing stimuli can be enhanced, this would be insufficient since the inducers are part of all possible stimulus interpretations. (c) The mechanism of Chong et al. cannot apply to Experiment 2. There we found an effect that was exactly opposite to what one would expect from a contrast-enhancement mechanism. When attention was drawn away from the stimulus, percept durations were significantly increased. Therefore, stimulus representations were actually weaker when attention was directed towards the motion quartet. This implies that quite different mechanisms are at play in ambiguous apparent motion and binocular rivalry.

So what are possible explanations for the effects of voluntary control and attention on the perception of the motion quartet? In Experiment 1, observers were able to change or hold their perception of movement with a high degree of control. It has been shown in electrophysiological (Martínez-Trujillo & Treue, 2002; Treue &

Martínez-Trujillo, 1999; Treue & Maunsell, 1996) and imaging studies (Beauchamp, Cox, & DeYoe, 1997; Muckli, Kohler, Kriegeskorte, & Singer, 2005; O'Craven, Rosen, Kwong, Treisman, & Savoy, 1997; Rees, Frith, & Lavie, 1997; Saenz, Buracas, & Boynton, 2002) that neuronal activity can be influenced substantially by the attentional focus of observers. Especially the electrode recordings by Treue and colleagues in the macaque monkey could establish that not only observers' spatial focus of attention has an influence but that there are also specific effects for certain motion directions, which could be confirmed for humans in psychophysical (Alais & Blake, 1999) and imaging experiments (Saenz et al., 2002). This means that we are able to selectively boost the representation of a certain direction of movement in a stimulus, comparable to the effect of spatial attention on stimuli presented at a certain location. This bias would be expected to be especially effective in determining conscious perception when a stimulus is ambiguous with respect to movement direction, as it is the case for the motion quartet. Slight increases in representation strength for one direction would tip the balance towards the intended percept. This effect might be especially strong for motion, since motion-processing areas show the highest degrees of attentional modulation (Muckli et al., 2005; O'Craven et al., 1997).

In Experiment 2, percept durations were increased by 70-80% on average when observers had to perform an attention-demanding task at fixation. A similar effect has been described for the motion aftereffect (Chaudhuri, 1990). In this study, the same center task as in our experiment was used to divert observers' attention from an adapting unidirectional motion stimulus. Compared to the passive-viewing condition, the duration of the following motion aftereffect was considerably reduced with the attention task, a result also confirmed in later studies (Georgiades & Harris, 2000; Georgiades & Harris, 2002b; Georgiades & Harris, 2002a; Lankheet & Verstraten, 1995; Rezec, Krekelberg, & Dobkins, 2004). Although the exact neuronal mechanisms of the motion aftereffect are not known yet (Culham, Dukelow, Vilis, Hassard, Gati, Menon, & Goodale, 1999; Huk, Ress, & Heeger, 2001; Tootell, Reppas, Dale, Look, Sereno, Malach, Brady, & Rosen, 1995; for a review see Anstis, Verstraten, & Mather, 1998), it is widely assumed that adaptation of direction-selective cells is the underlying cause. Adaptation processes have also often been adduced as explanation for percept changes in ambiguous apparent motion (Anstis, Giaschi, & Cogan, 1985; Clatworthy & Frisby, 1973; Finlay & von Grünau, 1987; Muckli et al., 2002; Selmes et al., 1997). For our results, this would imply that phase durations are prolonged by the attention task because adaptation for the perceived motion direction is reduced and therefore it takes more time to sufficiently reduce the strength of the dominant percept for a switch to occur. An alternative to the adaptation model has been proposed by Hock and colleagues (Hock, Schöner, & Hochstein, 1996). In their experiments, they found that adaptation might have a minor influence on perceptual switches in ambiguous apparent motion, but that the main causing factor is spontaneous activity fluctuations that can randomly tip the balance towards one percept or the other. On their account, a possible explanation for our results would be that diverting attention from the motion quartet in our experiments reduces the variance of spontaneous fluctuations and thereby leads, on average, to extended dominance durations.

In conclusion, we found substantial modulation of conscious perception of the motion quartet in a large sample of observers when they were instructed to voluntarily control the motion direction. Moreover, a comparably large effect was observed when their spatial attention was drawn away from the motion quartet. Voluntary control might be achieved through feature-selective attentional mechanisms that boost one stimulus interpretation over the alternative. The effect of

spatial attention can be explained by modulation of adaptation processes. When attention is drawn away, adaptation to the currently perceived motion direction is reduced, prolonging the phase duration of the dominant percept.

References

Alais, D., & Blake, R. (1999). Neural strength of visual attention gauged by motion adaptation. *Nat. Neurosci., 2*, 1015-1018.
Anstis, S.M., Giaschi, D., & Cogan, A.I. (1985). Adaptation to apparent motion. *Vision Res., 25*, 1051-1062.
Anstis, S.M., Verstraten, F.A.J., & Mather, G. (1998). The motion aftereffect. *Trends Cogn. Sci., 2*, 111-117.
Beauchamp, M.S., Cox, R.W., & DeYoe, E.A. (1997). Graded effects of spatial and featural attention on human area MT and associated motion processing areas. *J. Neurophysiol., 78*, 516-520.
Blake, R., Fox, R., & McIntyre, C. (1971). Stochastic properties of stabilized-image binocular rivalry alternations. *J. Exp. Psychol., 88*, 327-332.
Braddick, O.J. (1980). Low-level and high-level processes in apparent motion. *Philos. Trans. R. Soc. Lond. B Biol. Sci., 290*, 137-151.
Brascamp, J.W., van Ee, R., Pestman, W.R., & van den Berg, A.V. (2005). Distributions of alternation rates in various forms of bistable perception. *J. Vis., 5*, 287-298.
Carrasco, M., Ling, S., & Read, S. (2004). Attention alters appearance. *Nat. Neurosci., 7*, 308-313.
Chaudhuri, A. (1990). Modulation of the motion aftereffect by selective attention. *Nature, 344*, 60-62.
Chong, S.C., & Blake, R. (2006). Exogenous attention and endogenous attention influence initial dominance in binocular rivalry. *Vision Res., 46*, 1794-1803.
Chong, S.C., Tadin, D., & Blake, R. (2005). Endogenous attention prolongs dominance durations in binocular rivalry. *J. Vis., 5*, 1004-1012.
Clatworthy, J.L., & Frisby, J.P. (1973). Real and apparent visual movement: Evidence for a unitary mechanism. *Perception, 2*, 161-164.
Culham, J.C., Dukelow, S.P., Vilis, T., Hassard, F.A., Gati, J.S., Menon, R.S., & Goodale, M.A. (1999). Recovery of fMRI activation in motion area MT following storage of the motion aftereffect. *J. Neurophysiol., 81*, 388-393.
DeSilva, H.R. (1928). Kinematographic movement of parallel lines. *J. Gen. Psychol., 1*, 550-577.
Duncker, K. (1929). Über induzierte Bewegung. *Psychol. Forsch., 12*, 180-259.
Finlay, D., & von Grünau, M.W. (1987). Some experiments on the breakdown effect in apparent motion. *Percept. Psychophys., 42*, 526-534.
Georgiades, M.S., & Harris, J.P. (2000). The spatial spread of attentional modulation of the motion aftereffect. *Perception, 29*, 1185-1201.
Georgiades, M.S., & Harris, J.P. (2002a). Effects of attentional modulation of a stationary surround in adaptation to motion. *Perception, 31*, 393-408.
Georgiades, M.S., & Harris, J.P. (2002b). Evidence for spatio-temporal selectivity in attentional modulation of the motion aftereffect. *Spat. Vis., 16*, 21-31.
Hock, H.S., Schöner, G., & Hochstein, S. (1996). Perceptual stability and the selective adaptation of perceived and unperceived motion directions. *Vision Res., 36*, 3311-3323.
Hoeth, F. (1968). Bevorzugte Richtungen bei stroboskopischen Alternativbewegungen. *Psychol. Beiträge, 10*, 494-527.
Huk, A.C., Ress, D., & Heeger, D.J. (2001). Neuronal basis of the motion aftereffect reconsidered. *Neuron, 32*, 161-172.

Kenkel, F. (1913). Untersuchungen über den Zusammenhang zwischen Erscheinungsgröße und Erscheinungsbewegung bei einigen sogenannten optischen Täuschungen. *Z. Psychol., 67*, 358-449.
Korte, A. (1915). Kinematoskopische Untersuchungen. *Z. Psychol., 72*, 194-296.
Lack, L.C. (1971). The role of accommodation in the control of binocular rivalry. *Percept. Psychophys., **10***, 42.
Lankheet, M.J.M., & Verstraten, F.A.J. (1995). Attentional Modulation of Adaptation to 2-Component Transparent Motion. *Vision Res., 35*, 1401-1412.
Lehky, S.R. (1988). An astable multivibrator model of binocular rivalry. *Perception, 17*, 215-228.
Leopold, D.A., & Logothetis, N.K. (1999). Multistable phenomena: changing views in perception. *Trends Cogn. Sci., 3*, 254-264.
Levelt, W.J. (1967). Note on the distribution of dominance times in binocular rivalry. *Br. J. Psychol., 58*, 143-145.
Martínez-Trujillo, J.C., & Treue, S. (2002). Attentional modulation strength in cortical area MT depends on stimulus contrast. *Neuron, 35*, 365-370.
Meng, M., & Tong, F. (2004). Can attention selectively bias bistable perception? Differences between binocular rivalry and ambiguous figures. *J. Vis., 4*, 539-551.
Muckli, L., Kohler, A., Kriegeskorte, N., & Singer, W. (2005). Primary visual cortex activity along the apparent-motion trace reflects illusory perception. *PLoS Biol., 3*, e265.
Muckli, L., Kriegeskorte, N., Lanfermann, H., Zanella, F.E., Singer, W., & Goebel, R. (2002). Apparent motion: event-related functional magnetic resonance imaging of perceptual switches and states. *J. Neurosci., 22*, RC219 (1-5).
Murray, S.O., & Wojciulik, E. (2004). Attention increases neural selectivity in the human lateral occipital complex. *Nat. Neurosci., 7*, 70-74.
Neuhaus, W. (1930). Experimentelle Untersuchung der Scheinbewegung. *Arch. Gesamte Psychol., 75*, 315-458.
O'Craven, K.M., Rosen, B.R., Kwong, K.K., Treisman, A., & Savoy, R.L. (1997). Voluntary attention modulates fMRI activity in human MT-MST. *Neuron, 18*, 591-598.
Ramachandran, V.S., & Anstis, S.M. (1983). Perceptual organization in moving patterns. *Nature, 304*, 529-531.
Ramachandran, V.S., & Anstis, S.M. (1985). Perceptual organization in multistable apparent motion. *Perception, 14*, 135-143.
Rees, G., Frith, C.D., & Lavie, N. (1997). Modulating irrelevant motion perception by varying attentional load in an unrelated task. *Science, 278*, 1616-1619.
Rezec, A., Krekelberg, B., & Dobkins, K.R. (2004). Attention enhances adaptability: evidence from motion adaptation experiments. *Vision Res., 44*, 3035-3044.
Roget, P.M. (1825). Explanation of an optical deception in the appearance of the spokes of a wheel seen through vertical apertures. *Philos. Trans. R. Soc. Lond., 115*, 131-140.
Saenz, M., Buracas, G.T., & Boynton, G.M. (2002). Global effects of feature-based attention in human visual cortex. *Nat. Neurosci., 5*, 631-632.
Schiller, P.v. (1933). Stroboskopische Alternativversuche. *Psychol. Forsch., 17*, 179-214.
Sekuler, R. (1996). Motion perception: a modern view of Wertheimer's 1912 monograph. *Perception, 25*, 1243-1258.
Selmes, C.M., Fulham, W.R., Finlay, D.C., Chorlton, M.C., & Manning, M.L. (1997). Time-till-breakdown and scalp electrical potential maps of long-range apparent motion. *Percept. Psychophys., 59*, 489-499.

Steinman, R.M., Pizlo, Z., & Pizlo, F.J. (2000). Phi is not beta, and why Wertheimer's discovery launched the Gestalt revolution. *Vision Res., 40*, 2257-2264.
Sterzer, P., & Kleinschmidt, A. (2005). A neural signature of colour and luminance correspondence in bistable apparent motion. *Eur. J. Neurosci., 21*, 3097-3106.
Suzuki, S., & Peterson, M.A. (2000). Multiplicative effects of intention on the perception of bistable apparent motion. *Psychol. Sci., 11*, 202-209.
Tootell, R.B.H., Reppas, J.B., Dale, A.M., Look, R.B., Sereno, M.I., Malach, R., Brady, T.J., & Rosen, B.R. (1995). Visual motion aftereffect in human cortical area MT revealed by functional magnetic resonance imaging. *Nature, 375*, 139-141.
Treue, S., & Martínez-Trujillo, J.C. (1999). Feature-based attention influences motion processing gain in macaque visual cortex. *Nature, 399*, 575-579.
Treue, S., & Maunsell, J.H.R. (1996). Attentional modulation of visual motion processing in cortical areas MT and MST. *Nature, 382*, 539-541.
van Dam, L.C., & van Ee, R. (2005). The role of (micro)saccades and blinks in perceptual bi-stability from slant rivalry. *Vision Res., 45*, 2417-2435.
van Dam, L.C., & van Ee, R. (2006). The role of saccades in exerting voluntary control in perceptual and binocular rivalry. *Vision Res., 46*, 787-799.
van Ee, R. (2005). Dynamics of perceptual bi-stability for stereoscopic slant rivalry and a comparison with grating, house-face, and Necker cube rivalry. *Vision Res., 45*, 29-40.
van Ee, R., van Dam, L.C., & Brouwer, G.J. (2005). Voluntary control and the dynamics of perceptual bi-stability. *Vision Res., 45*, 41-55.
van Ee, R., van Dam, L.C., & Erkelens, C.J. (2002). Bi-stability in perceived slant when binocular disparity and monocular perspective specify different slants. *J. Vis., 2*, 597-607.
Wertheimer, M. (1912). Experimentelle Studien über das Sehen von Bewegung. *Z. Psychol., 61*, 161-265.

CHAPTER 6

Continuous Visibility of Stimulus Parts Does Not Enhance Voluntary Control of Binocular Rivalry

Based on:

Data from a collaborative project with Prof. Frank Tong (Vanderbilt University, Nashville, TN) and Dr. Ming Meng (Massachusetts Institute of Technology, Cambridge, MA).

Abstract

In previous studies, it could be demonstrated that the amount of selective voluntary control observers can exert on the perception of a binocular-rivalry display is very limited. Specifically, observers cannot increase or decrease the dominance durations of a percept when instructed to do so. If attention is involved in the process of voluntary control, the question arises whether visibility of a stimulus is a prerequisite for effective operation of attentional mechanisms. If visibility is necessary, this might explain why control is reduced in rivalry displays because input through one eye is suppressed and invisible during major parts of the stimulus presentation time. In our study, we wanted to test the hypothesis that visibility enhances the operation of voluntary control and devised a new binocular-rivalry display where the outer parts of our grating stimuli where almost continuously visible while rivalry was instigated at the center part of the display (Edge stimulus). Observers were instructed to hold one percept as long as possible during prolonged presentation and to pay attention to the outer visible part of the desired stimulus to boost its dominance. Voluntary control during Edge-stimulus presentation was compared to a Center stimulus where only the rivaling center part was presented. In both naïve and expert observers, the amount of control they could exert was negligible and there was no significant difference between Edge and Center stimulus. To control for ceiling effects, we tested in the expert observers how shifts of fixation would influence dominance durations. The increase in dominance durations was significantly larger for the Fixation condition compared to the Edge and Center stimulus, suggesting that larger modulation strengths can be achieved through overt shifts of attention. We conclude that reduced visibility does not explain the limited control naïve and expert observers have of binocular-rivalry displays. This supports the conclusion of previous studies that the mechanisms governing competition in binocular rivalry are relatively immune to top-down influence from selective attentional mechanisms.

Introduction

Binocular rivalry is a competitive visual process that occurs when different pictures are presented to the two eyes. At any time, observers typically perceive only one of the two pictures with frequent switches between the possible stimulus interpretations (Wheatstone, 1838). There is a debate on where in the visual system binocular rivalry is resolved, in early (Blake, 1989; Tong & Engel, 2001; Haynes, Deichmann, & Rees, 2005; Lee, Blake, & Heeger, 2005; Wunderlich, Schneider, & Kastner, 2005) or later stages of processing (Leopold & Logothetis, 1996; Logothetis, Leopold, & Sheinberg, 1996; Sheinberg & Logothetis, 1997; but see Blake & Logothetis, 2002). Different levels of the visual hierarchy show varying amounts of susceptibility to top-down influence from attentional mechanisms. Typically, higher areas display considerably stronger modulation than early areas. (Kastner, De Weerd, Desimone, & Ungerleider, 1998; Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999; Kastner & Ungerleider, 2001). Therefore, the site of resolution for binocular rivalry might also determine the susceptibility of rivalry to attentional influence. Conversely, psychophysically probing the amount of attentional modulation could give a hint to the cortical stage on which rivalry is resolved.

Several studies have addressed the issue of how much binocular rivalry can be manipulated by attention. Already Helmholtz (1866) described that he could prolong dominance durations by focusing on a specific percept. Other studies showed that the alternation rate during rivalry could be increased as well as decreased non-selectively when observers were instructed accordingly (Meredith & Meredith, 1962; Lack, 1978; Meng & Tong, 2004; van Ee, van Dam, & Brouwer, 2005). Also, initial dominance during rivalry can be influenced by the preceding attentional focus (Ooi & He, 1999; Chong & Blake, 2006). In contrast, two of the above studies also investigated the effect of selective attention – holding a specific percept – on dominance durations and did not find a substantial effect of attention for binocular rivalry but stronger effects for other multistable phenomena like the Necker cube and slant rivalry (Meng & Tong, 2004; van Ee et al., 2005). This apparent difference between results was resolved in a recent study by Chong and colleagues (Chong, Tadin, & Blake, 2005). They were able to demonstrate that a selective enhancement of dominance durations for a given percept could only be achieved when an attention-demanding task had to be performed on the relevant stimulus dimension. When the stimulus dimension was irrelevant, there was no effect on dominance durations. Interestingly, the enhancement effect could be mimicked by increasing the contrast of the respective stimulus only during dominance phases, i.e., when the stimulus was consciously perceived.

The above results by Chong and colleagues (2005) suggest that attention can only operate on consciously perceived stimuli during binocular rivalry. Therefore, it is possible that observers' ability to selectively hold a percept is limited by the intermittent visibility of the stimulus. In our experiments, we wanted to investigate whether continuous visibility of parts of a binocular-rivalry display might provide observers with an enhanced leverage on the conscious perception of the stimulus. We compared voluntary control over a standard grating stimulus producing complete rivalry with voluntary control over a new grating stimulus with rivalry only in the center of the display and continuously visible edges. Before a trial, observers were instructed to hold one of the two possible percepts or passively view the display. For naïve as well as expert observers, there was no significant difference between the complete- and partial-rivalry conditions. This suggests that continuous visibility of

stimulus parts does not enhance the effectiveness of attentional mechanisms during binocular rivalry.

Methods

Observers

21 undergraduate students from Vanderbilt University (age, 18-22) participated in the experiments. The participants received course credit for their participation and were naïve with respect to the purpose of the study. Eight experienced observers (age, 22-31) were recruited for the same tasks and an additional control experiment (see below). All observers had normal or corrected-to-normal vision and gave their informed consent in accordance with the rules of the Institutional Review Board at Vanderbilt University.

Stimuli and Apparatus

All stimuli were presented on a CRT monitor and programmed using Matlab with the Psychophysics Toolbox extensions (Brainard, 1997; Pelli, 1997). Stimuli were red and green isoluminant (4.9 cd/m^2) sinusoidal gratings with an orientation of 45° (Fig. 1). The green grating (right eye) was tilted to the left and the red grating (left eye) to the right. There were three different stimulus versions: (a) The **Center stimulus** was 2° wide and 3.7° long surrounded by a white rectangular frame. Grating contrast in the center region was varied in discrete steps from 90% to 10%. The polarity of the

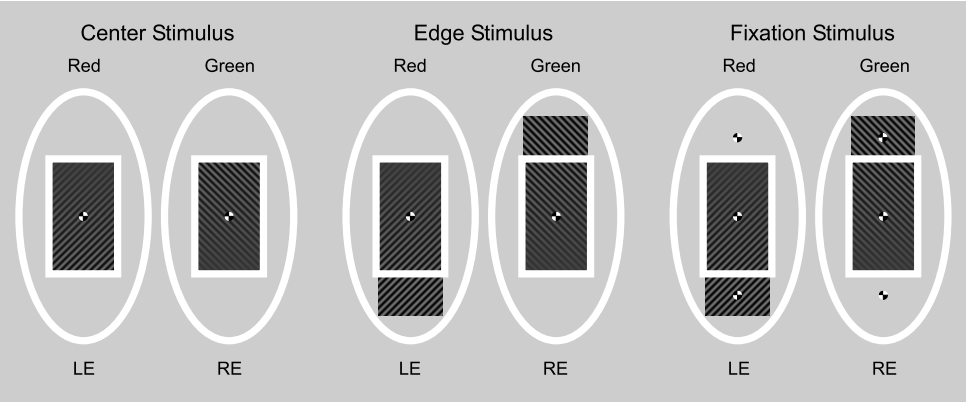

Figure 1. Stimuli for the different conditions. Stimuli presented to the left (LE) and right eye (RE) for conditions C*enter stimulus*, E*dge stimulus*, and *Fixation stimulus*. For the *Fixation stimulus*, the three possible locations of the fixation spot are marked. For details, see Methods section.

contrast gradient was opposite for the red (increasing contrast from top to bottom) and green grating (decreasing contrast from top to bottom). (b) The **Edge stimulus** consisted of the Center stimulus plus additional red and green gratings at the top and bottom (90% contrast). The top and bottom parts were only presented to one eye (green top part to the right eye and red bottom part to the left eye). The size of the outer gratings was 2° × 1.3°. (c) The **Fixation stimulus** was identical with the Edge stimulus, only the fixation position was shifted between three positions in different

trials. The fixation spot could be located in the center of either the middle, lower (2.5° down), or upper grating region (2.5° up). The Fixation stimulus was only tested with the expert observers.

For all stimulus types, the fixation position was indicated by a circle with black and white quarter segments (diameter, 0.4°). The background was uniform gray (5.3 cd/m^2). For better fusion of the images, the gratings were surrounded by a white ellipse (6.3° x 9.2°; line thickness, 0.2°; luminance, 89.8 cd/m^2).

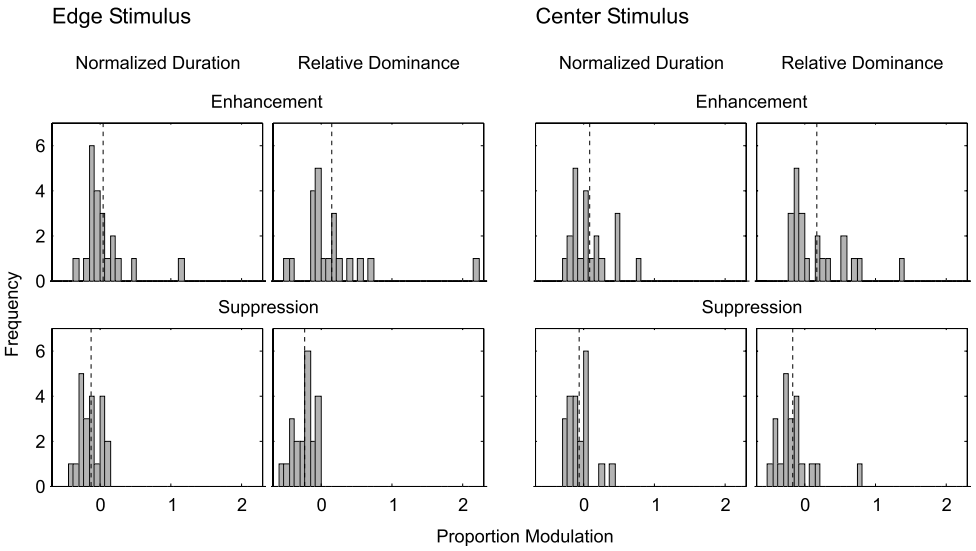

Figure 2. Distribution of modulation values across naïve observers (N=21). Histograms of relative modulation for enhancement and suppression for normalized duration and relative dominance and the two stimulus types (Edge/Center stimulus). The black dashed lines indicate the respective mean values.

Procedure

All procedures were approved by the Institutional Review Board at Vanderbilt University. The images were presented to the two eyes through a custom-made mirror stereoscope (Ed Optics). Before each session, mirrors were adjusted for individual participants to allow optimal fusion between the eyes. Basic stereo vision was assessed with a random-dot stereogram. Participants received an instruction sheet explaining the phenomenon of binocular rivalry and the different task conditions. In two preliminary trials, participants were familiarized with the binocular-rivalry stimulus and the report procedure. The dominance phases were indicated with three different keys corresponding to complete perception of the red grating, complete perception of the green grating, and a mix of the two. Six additional practice trials were used to acquaint participants with the six experimental conditions (two stimulus types times three possible instructions). Each trial lasted 60 seconds. Participants were instructed to keep fixation at all times and not to use eye blinks for their task. The three different attentional-control conditions were indicated by a letter

below the fixation spot before the trial started. The instructions for the different conditions were as follows: (1) **Passive** – Please keep your eyes focused steadily on the fixation spot throughout each 1 minute trial, and passively report any change of percept of the stripes in the central rectangular region by pressing one of three keys. Let your perceptual impressions change automatically and spontaneously (do not try to control or alter what you perceive). (2) + (3) **Hold Red/Green** – Please keep your eyes focused steadily on the fixation spot and try to hold onto your perception of the red stripes or the green stripes for as long as possible. It might be useful to attend to the lower (red) or upper (green) part of the stripes. This can be done by keeping your eyes fixed on the fixation spot while focusing your mental concentration on the high-contrast portion of the stripes that lies at the bottom (red) or top (green) of the visual display. Report any change of percept in the central region with the three keys.

The six trial types were presented in random order in blocks of 12 trials. Naïve observers performed two blocks of trials (four trials per condition). Expert observers completed four blocks of trials for the Edge and Center stimulus and two blocks for the Fixation condition (eight trials per condition). With the Fixation stimulus, experts had the instruction to hold their gaze at the respective fixation location at any time. After the experiment, participants were debriefed and asked about any additional strategy they used for control of the rivaling displays as well as about their subjective assessment of the control they could exert.

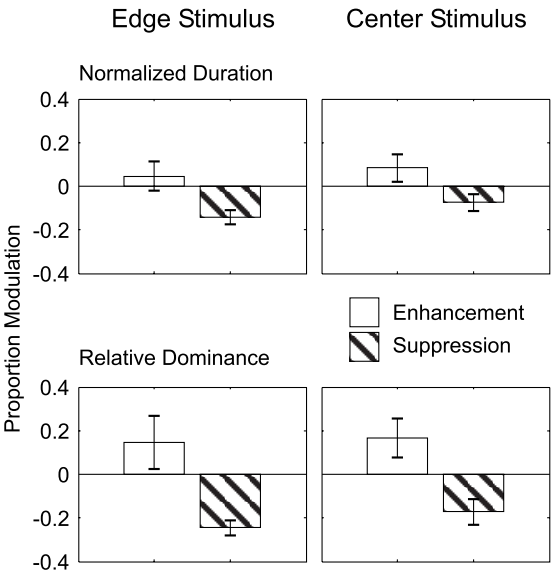

Figure 3. Average modulation for naïve observers (N=21). Group averages of percept enhancement (red bars) and suppression (green bars) for normalized duration and relative dominance and the two stimulus types (Edge/Center stimulus). Error bars indicate standard errors of the mean.

Data Analysis

Data were analyzed with the software packages SPSS 12.0 (SPSS, Inc., Chicago, IL, United States of America) and Matlab 7.0.4.365 (The MathWorks, Inc., Natick, MA, United States of America). For every two-minute trial, the first two dominance durations were discarded. For display purposes and statistical analyses, dominance durations were normalized by the mean dominance duration across all conditions (excluding phases of mixed percepts) for each participant. In addition, the effects on

relative dominance (percentage of red/green dominance for a two-minute trial) were assessed. For the statistical analysis, percent change values were calculated relative to the passive condition. Change values were averaged across the trial types Hold Red/Hold Green in single participants, resulting in the two dependent variables "enhancement of the desired percept" (red percept during Hold Red trials and green percept during Hold Green trials) and "suppression of the undesired percept" (red percept during Hold Green trials and green percept during Hold Red trials), and then group-analyzed. The same calculation procedures were applied to the data of the Fixation stimulus. In this case, the enhancement and suppression conditions were not defined by instruction but by the location of the fixation spot, e.g., the condition where the fixation spot was placed in the upper green grating edge was corresponding to the "Hold Green" instruction.

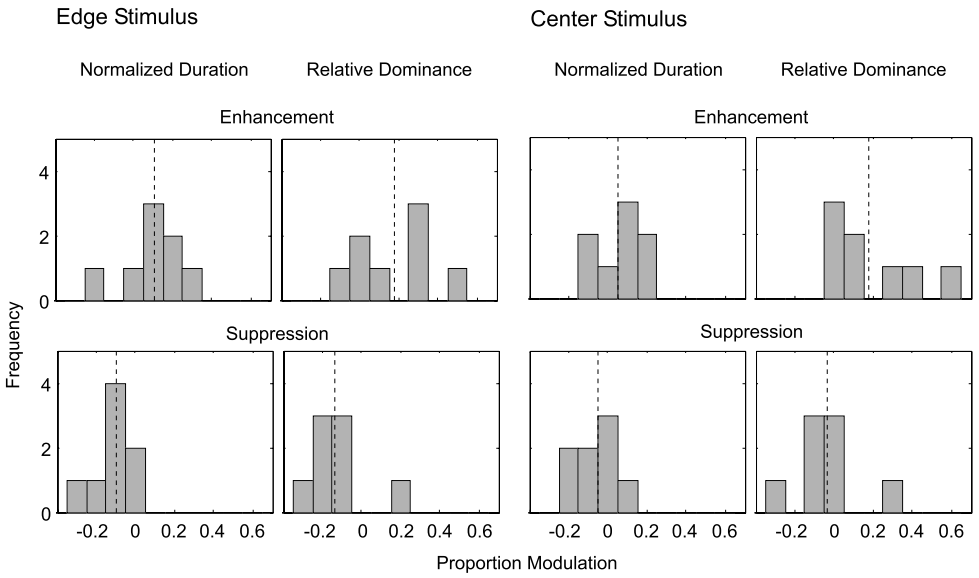

Figure 4. Distribution of modulation values for Edge and Center stimulus across expert observers (N=8). Histograms of modulation for enhancement and suppression for normalized duration and relative dominance. The black dashed lines indicate the respective mean values.

Results

Naïve Observers

Mean dominance durations for perception of a pure red, pure green, and mixed green/red grating for passive viewing were 2.2 s, 1.9 s, and 1.7 s, respectively. The participants' ability to enhance the perception of the desired percept (e.g., 'red' for the instruction 'Hold Red') and to suppress the perception of the non-desired percept (e.g., 'green' for the instruction 'Hold Red') were analyzed separately. Those two aspects of voluntary control are not necessarily confounded. In our data set,

enhancement and suppression values were uncorrelated across observers for the two stimulus types (Edge/Center stimulus) and for the two dependent measures (normalized duration and relative dominance) ($r < .38$, $p > .09$). The ability to modulate perception of the Edge and Center stimuli was highly correlated across naïve observers ($p < 0.005$), except for the suppression value of normalized durations ($r(21) = .01$, $p = .963$). The amount of control varied widely between participants (Fig. 2). Several observers were unable to influence the perception in the desired direction.

On average, naïve observers could enhance and suppress the duration of the desired percept only by around 10% for normalized durations and around 20% for relative dominance (Fig. 3). For all measures, there was no significant difference between the change values for Edge and Center stimuli ($p > .135$).

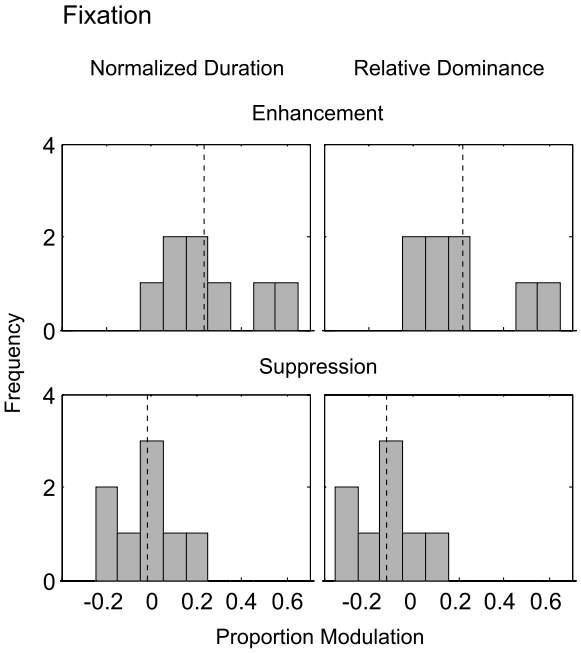

Figure 5. Distribution of modulation values for Fixation condition across expert observers (N=8). Histograms of modulation for enhancement and suppression for normalized duration and relative dominance. The black dashed lines indicate the respective mean values.

Expert Observers

Mean dominance durations for perception of the red, green, and mixed grating for passive viewing were 1.8 s, 1.7 s, and 1.2 s. Also for the experts, the correlations between enhancement and suppression across participants were not significant ($p > .05$). The ability to modulate the Edge and the Center stimulus was highly correlated, except for the suppression value of the normalized durations ($r = .44$, $p = .27$).

In addition to the Edge and Center stimulus, expert observers were also tested with the Fixation condition to get an estimate of how strong the modulation of percept durations can be with an exogenous manipulation of attention (Fig. 4+5). To assess differences in modulation across all three stimulus types, repeated-measures ANOVAs with Huynh-Feldt correction were performed separately for enhancement

and suppression as well as for the two different dominance measures (normalized duration/relative dominance).

The expert observers could enhance and suppress normalized durations by around 10% for the Edge and Center stimulus. For relative dominance, enhancement was almost 20% and suppression was at 10% and below (Fig. 6). For the Fixation stimulus, the pattern was different: Relative dominance values were similar to the Edge and Center stimulus, but enhancement for normalized durations was 24% and suppression just below zero. The only significant difference between stimulus types was found for the enhancement of normalized durations, $F(1.739, 12.171) = 5.738$, $p = .02$, suggesting that the enhancement through fixation was larger than for the Edge and Center stimuli. All other ANOVAs were non-significant ($p > .28$).

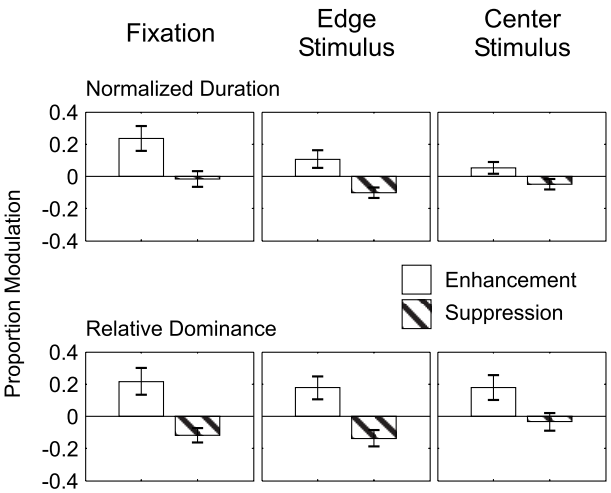

Figure 6. Average modulation for expert observers (N=8). Group averages of percent enhancement (red bars) and suppression (green bars) for normalized duration and relative dominance and the three stimulus types (Edge/Center/Fixation stimulus). Error bars indicate standard errors of the mean.

Discussion

We investigated the relevance of stimulus visibility for voluntary control of a binocular-rivalry display in naïve and expert observers. The continuous visibility of the target's outer edges did not enhance the ability of participants to keep the desired and suppress the undesired percept. This was true for normalized durations as well as relative dominance. Expert observers were tested with an additional stimulus, where percept dominance was influenced by shifting the fixation spot to the outer grating parts. This exogenous manipulation of attention had a significantly stronger effect on the enhancement of dominance durations than instructions for the Edge and Center conditions, suggesting that the lack of voluntary control is not attributable to a ceiling effect.

Our results confirm previous reports that the ability to selectively enhance a percept during binocular rivalry is very limited (Meng & Tong, 2004; van Ee et al., 2005). We also extend those findings by showing that stimulus visibility is not the limiting factor for the operation of voluntary attention. How do our data relate to other

studies in which substantial modulation of binocular rivalry was reported? There are four dimensions on which the relevant experiments can be organized: (a) Duration of the rivaling stimuli. Some experiments used continuous rivalry (Helmholtz, 1866; Meredith & Meredith, 1962; Lack, 1978; Meng & Tong, 2004; Chong et al., 2005; van Ee et al., 2005) and others only tested initial dominance or very short presentations (Ooi & He, 1999; Mitchell, Stoner, & Reynolds, 2004; Chong & Blake, 2006). For short durations, all studies reported substantial impact through voluntary attention, whereas for continuous rivalry results were variable. (b) Attentional source. Studies differ in the way they manipulated attention, either endogenously by mere instructions to the observers (Helmholtz, 1866; Meredith & Meredith, 1962; Lack, 1978; Ooi & He, 1999; Meng & Tong, 2004; Chong et al., 2005; van Ee et al., 2005; Chong & Blake, 2006) or exogenously by using pop-out elements or contrast increments (Ooi & He, 1999; Mitchell et al., 2004; Chong & Blake, 2006). For both types of attentional source, modulation effects were described but not for all experiments with endogenous attention. Moreover, all experiments with exogenous cueing used short presentation durations, which can be expected, since any effect of a transient cue would dissipate quickly during sustained rivalry. (c) Task demand. Chong and colleagues (2005) reported that for the effectiveness of endogenous attention, it was necessary that observers were engaged in an attention-demanding task on the relevant stimulus. An explicit task was also used in previous studies showing attentional modulation of rivalry (Helmholtz, 1866). Other studies did not have an explicit task on the stimuli besides the instruction to influence the percept (Meredith & Meredith, 1962; Lack, 1978; Ooi & He, 1999; Meng & Tong, 2004; Mitchell et al., 2004; van Ee et al., 2005; Chong & Blake, 2006). In those experiments, results for attentional modulation were inconsistent probably depending on other relevant factors. (d) Selectivity of attention. Influence on conscious perception during binocular rivalry can be selective for percepts, e.g., by instructing observers to hold one specific stimulus interpretation, or non-selective, e.g., by instructing observers to speed up alternation between percepts. Some experiments manipulated attention to enhance percepts in a selective manner (Helmholtz, 1866; Meng & Tong, 2004; Mitchell et al., 2004; Chong et al., 2005; van Ee et al., 2005; Chong & Blake, 2006) and others non-selectively (Meredith & Meredith, 1962; Lack, 1978; Meng & Tong, 2004; van Ee et al., 2005). On average non-selective manipulation was more effective than selective influence.

Although there is no single study that systematically varied all the factors mentioned above, a clear picture emerges if the results from the cited experiments are combined. The characteristics promoting effectiveness of attention are short stimulus duration/initial dominance, exogenous attention (though it was always confounded with short duration in the studies described), task demand on relevant stimulus dimension, and non-selectivity of attentional instruction.

An interesting aspect of our results was that the values for enhancement of the desired percept and suppression of the non-desired percept were not correlated in both the naïve and expert observers. A priori, one might assume that those two variables are both determined by a single underlying factor representing an observer's ability to exert attentional control. But according to our data, there is already a divergence for different measures of attentional control in a single paradigm. It would be interesting to test observers in multiple paradigms with different instructions to investigate how different measures of voluntary attention cluster across various multistable stimuli. Possibly, mechanisms of voluntary attention show a subdifferentiation according to the specific neural substrates they depend on. In a different context, different subdivisions of attentional capacities have been developed

and related to the respective neural mechanisms (Posner & Petersen, 1990; Corbetta & Shulman, 2002). An alternative explanation for the lack of correlation between the two measures of attentional control could be that observers used different strategies to implement the instruction of voluntary control. If most of the observers focused on one aspect of control, predominantly enhancing the desired or suppressing the non-desired percept, then this would lead to a very weak correlation between the two measures. Such a variation of strategies between observers was not apparent from our debriefing protocols, in which we explicitly asked for the strategies observers employed during the Hold conditions. In addition, every participant was extensively instructed on the task and we had test trials for every single condition to ensure that participants performed consistently.

In conclusion, we could demonstrate that continuous visibility of stimulus parts does not enhance attentional control of conscious perception during binocular rivalry. This cannot be explained by a ceiling effect. Shifts of fixation position did lead to a significantly stronger enhancement of percept durations, suggesting that factors other than voluntary attention are able to promote percept durations if appropriately manipulated. Interestingly, measures for enhancement of the desired percept and suppression of the undesired percept were uncorrelated in our data set. Further studies are needed in which task instructions for enhancement and suppression are explicitly controlled. If the two measures can be disentangled psychophysically, this would indicate an important subdivision of attentional mechanisms for the control of ambiguous stimuli.

Acknowledgments

We thank Emma Ferneyhough and John Dewey for their support with conducting the experiments.

References

Blake, R. (1989). A neural theory of binocular rivalry. *Psychol. Rev., 96*, 145-167.
Blake, R., & Logothetis, N.K. (2002). Visual competition. *Nat. Rev. Neurosci., 3*, 13-21.
Brainard, D.H. (1997). The Psychophysics Toolbox. *Spat. Vis., 10*, 433-436.
Chong, S.C., & Blake, R. (2006). Exogenous attention and endogenous attention influence initial dominance in binocular rivalry. *Vision Res., 46*, 1794-1803.
Chong, S.C., Tadin, D., & Blake, R. (2005). Endogenous attention prolongs dominance durations in binocular rivalry. *J. Vis., 5*, 1004-1012.
Corbetta, M., & Shulman, G.L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nat. Rev. Neurosci., 3*, 201-215.
Haynes, J.-D., Deichmann, R., & Rees, G. (2005). Eye-specific effects of binocular rivalry in the human lateral geniculate nucleus. *Nature, 438*, 496-499.
Helmholtz, H.v. (1866). *Handbuch Der Physiologischen Optik*. Hamburg: Voss.
Kastner, S., De Weerd, P., Desimone, R., & Ungerleider, L.G. (1998). Mechanisms of directed attention in the human extrastriate cortex as revealed by functional MRI. *Science, 282*, 108-111.
Kastner, S., Pinsk, M.A., De Weerd, P., Desimone, R., & Ungerleider, L.G. (1999). Increased activity in human visual cortex during directed attention in the absence of visual stimulation. *Neuron, 22*, 751-761.
Kastner, S., & Ungerleider, L.G. (2001). The neural basis of biased competition in human visual cortex. *Neuropsychologia, 39*, 1263-1276.
Lack, L. (1978). *Selective Attention and the Control of Binocular Rivalry*. The Hague: Mouton.
Lee, S.H., Blake, R., & Heeger, D.J. (2005). Traveling waves of activity in primary visual cortex during binocular rivalry. *Nat. Neurosci., 8*, 22-23.
Leopold, D.A., & Logothetis, N.K. (1996). Activity changes in early visual cortex reflect monkeys' percepts during binocular rivalry. *Nature, 379*, 549-553.
Logothetis, N.K., Leopold, D.A., & Sheinberg, D.L. (1996). What is rivalling during binocular rivalry? *Nature, 380*, 621-624.
Meng, M., & Tong, F. (2004). Can attention selectively bias bistable perception? Differences between binocular rivalry and ambiguous figures. *J. Vis., 4*, 539-551.
Meredith, G.M., & Meredith, C.G. (1962). Effect of instructional conditions on rate of binocular rivalry. *Percept. Mot. Skills, 15*, 655-664.
Mitchell, J.F., Stoner, G.R., & Reynolds, J.H. (2004). Object-based attention determines dominance in binocular rivalry. *Nature, 429*, 410-413.
Ooi, T.L., & He, Z.J. (1999). Binocular rivalry and visual awareness: the role of attention. *Perception, 28*, 551-574.
Pelli, D.G. (1997). The VideoToolbox software for visual psychophysics: transforming numbers into movies. *Spat. Vis., 10*, 437-442.
Posner, M.I., & Petersen, S.E. (1990). The attention system of the human brain. *Annu. Rev. Neurosci., 13*, 25-42.
Sheinberg, D.L., & Logothetis, N.K. (1997). The role of temporal cortical areas in perceptual organization. *Proc. Natl. Acad. Sci. USA, 94*, 3408-3413.
Tong, F., & Engel, S.A. (2001). Interocular rivalry revealed in the human cortical blind-spot representation. *Nature, 411*, 195-199.
van Ee, R., van Dam, L.C., & Brouwer, G.J. (2005). Voluntary control and the dynamics of perceptual bi-stability. *Vision Res., 45*, 41-55.

Wheatstone, C. (1838). Contributions to the physiology of vision. Part the first. On some remarkable, and hitherto unobserved, phenomena of binocular vision. *Phil. Trans. R. Soc. Lond., 128*, 371-394.

Wunderlich, K., Schneider, K.A., & Kastner, S. (2005). Neural correlates of binocular rivalry in the human lateral geniculate nucleus. *Nat. Neurosci., 8*, 1595-1602.

Summary

The focus of the work described in this thesis is bipartite: First, regarding content, the goal of our research was to investigate which neural mechanisms are involved in the generation of conscious movement perception and how these mechanisms are modulated by attention. Second, in terms of methods, we explored the potential of combining correlation and interference methods in functional brain imaging to describe the spatial and temporal characteristics of human visual cognition. The triad of methods included psychophysics, functional magnetic resonance imaging (fMRI), and transcranial magnetic stimulation (TMS). We showed how all these techniques contribute their unique informational content to the understanding of the brain's workings. Psychophysical measures provide a basic concept of the phenomenon and its dynamics, fMRI reveals the correlational structure between stimuli/tasks and neural activity, and TMS supplies a means to selectively interfere with processing in specific cortical loci. These approaches can not only be used in separate experiments but can also be valuably combined in a single study. Each experiment described in the previous chapters made its own contribution to the questions defined above. At the same time, each experiment was also biased more towards either the content or methods aspect, but taken together our results provide a coherent picture of the way different neuroscientific methods can be combined to study the neural correlates of human visual cognition.

In Chapter 2, we reported a study that investigated the neural correlates of long-range apparent motion in primary visual cortex (V1) using fMRI. In previous work, it could be demonstrated that the human MT/V5 complex (hMT/V5+), which is vital for motion processing, shows an increased response when objects are connected through apparent motion compared to statically flickering objects at the same locations. This is even the case when the motion and flickering conditions are not defined by different stimulus parameters but only by spontaneous changes of conscious perception during physically identical stimulation. We extended these findings by showing that, in addition to area hMT/V5+, also V1 is involved in the representation of apparent motion, specifically in the representation of the physically not existing path of movement. Since V1 is retinotopically organized with a high spatial resolution of its neuronal elements, we were able to separate stimulus representations and the representation of the illusory path. In conditions where apparent motion was seen, there was significant activation in brain regions representing the path, although they were not directly driven by the inducing squares. Since our apparent-motion stimulus spanned a large region of visual space, our interpretation of the data was that hMT/V5+ integrates the inducing objects and represents the motion aspect of the stimulus. The activity in V1 is then produced through feedback mechanisms driven by hMT/V5+. Only through the recurrent interaction between different regions our fully-fledged conscious perception is generated, where different stimulus aspects get represented by different cortical areas.

The experiment described in Chapter 3 investigated the dynamics of motion processing in hMT/V5+ using single-pulse TMS. With single-pulse TMS it is possible to probe the relevant time windows for processing in an area with millisecond precision. This means that in addition to the causal relevance of an area, also the timing of processing can be inferred. For hMT/V5+ and motion perception, there had been conflicting results in the literature concerning the time of maximal TMS interference. One group found a very early time window around stimulus onset, which

they interpreted as a hint for a fast route of processing through hMT/V5+ mediated via subcortical centers. An alternative pattern of results was described in another set of studies. The time window described there was much later, 100-150 ms after stimulus onset. This would concur more with EEG and MEG findings of motion processing in hMT/V5+. A shortcoming of the above studies was that the exact targeting of hMT/V5+ was never confirmed on independent grounds. The localization had usually been done with rules of thumb, starting from standard EEG electrode positions. Since hMT/V5+ is small in size and has a highly variable localization across individuals, it is of paramount importance to have an exact method for targeting hMT/V5+. Therefore, it was our approach to identify hMT/V5+ in individual participants with fMRI in a preliminary session. We then applied a stereotaxic positioning system we had developed previously to apply TMS to the individually defined hMT/V5+. We tested almost all possible time windows – in 10 ms steps – from -50 ms to 200 ms relative to stimulus onset. At these time points, single pulses of TMS were applied while subjects performed a random-dot motion discrimination task. Our results showed that there was a significant impairment of performance at 130-150 ms after stimulus onset confirming the results of the second group. But there was no effect in any individual for the 0 ms time window described by the first group. The study shows how MRI techniques can be used to apply TMS to specific target sites in individual participants. Only through independent confirmation of the TMS-coil localization relative to functionally defined brain regions, an objective methodology for coil placement can be achieved.

The experiments described in the two previous chapters demonstrated the unique contributions that fMRI and TMS can make independently and when combined in succession. In the fourth chapter, we explored the potential of simultaneously combining fMRI and TMS. The technique of applying magnetic stimulation in the scanner has only been developed in recent years. The first studies in this field focused on improving the setup and used simple paradigms, mainly in the motor system, to validate their techniques. In our study, we wanted to extend the application of the fMRI/TMS combination to more cognitive tasks. The functional impairment induced by TMS during such tasks has been termed ‘virtual lesion’, but up to now the neuronal consequences of these impairments could not be demonstrated. Therefore, it was our goal to visualize the effects of TMS – in terms of blood-oxygenation-level-dependent (BOLD) signal enhancement or suppression – with concurrent fMRI and compare those changes to the measured behavior of the participants. We used a visuospatial task that had been investigated in previous fMRI and TMS studies, in which processing essentially depends on activity in the superior parietal cortices. In this task, participants had to judge the angle of a shortly presented analog clock. As a control condition for unspecific TMS effects, we used a color discrimination task on the same stimulus material. In separate sessions, TMS was applied to right and left parietal cortex (electrode positions ‘P4’ and ‘P3’, respectively) during scanning. For right-parietal stimulation, we found a suppression of the BOLD response at the stimulated site but also in remote areas presumably connected to parietal cortex, especially the middle frontal gyrus. Notably, this suppression was also observable for the color task but to a much lesser degree. Only for the angle task and only for the superior parietal lobe and middle frontal gyrus, there was a very high correlation between the BOLD effect and the behavioral impairment. The behavioral impairment, measured as increased reaction times, was also only significant in the angle task. In contrast, left-parietal stimulation did not have any of these consequences, suggesting a right-parietal specialization for visuospatial processing. Apart from the hemispheric specialization, our data indicate that TMS

effects are not confined to the stimulated site but can be observed in a network of connected areas that are presumably relevant for the performed task. In addition, it is clear that TMS at a specific site does not necessarily result in a modulation of the BOLD signal: Left-parietal stimulation did not produce an observable BOLD reduction whatsoever. This would imply that a BOLD effect is only visible if the stimulated area is essential for the task or that the disturbance of the network activity could be alleviated through compensatory mechanisms in other brain areas.

The studies in the last two thesis chapters were concerned with a recent debate in philosophy as well as neuroscience quarters regarding the relationship between attention and consciousness. Traditionally, the two phenomena were considered inextricably linked: One could not be aware of something that was not attended. But several authors have argued that there is an important distinction to be made between the two, on conceptual grounds as well as for empirical reasons. Data from different experiments show that it is possible to disentangle the effects of attention and consciousness and argue for a relative independence of the underlying mechanisms. The last two thesis chapters focused on exploring psychophysically the interaction between attention and consciousness, specifically the amount of control we have with respect to our conscious perception of ambiguous stimulus displays. The two series of experiments used different paradigms – apparent motion and binocular rivalry – that have both been studied extensively in experiments investigating the neural correlates of visual awareness.

In Chapter 5, we used the so-called 'motion quartet', an apparent-motion stimulus that induces a perception of either horizontal or vertical movement. The currently perceived movement direction can change spontaneously, probably due to adaptation mechanisms. In two experiments, we investigated how observers can manipulate their perception depending on the received instruction and how manipulation of spatial attention affects the occurrence of spontaneous changes. In Experiment 1, participants were instructed either to speed up the alternation, to view the stimulus passively, or to slow down alternations. The amount of control observers displayed was substantial: They were able to almost double (or halve) the percept durations relative to passive viewing. Further analyses indicated that the temporal dynamics of alternations were similar across conditions, suggesting that spontaneous changes still occurred so that percept control was not completely determined by the observer's will. In the second experiment, spatial attention was diverted from the stimuli through an attention-demanding detection task at fixation. At the same time, participants still had to report on their conscious perception while they performed the task. When attention was distracted from the motion quartet, percept durations were increased by about 80% on average. That means when spatial attention is drawn away from the stimuli, the current percept is stabilized. A possible interpretation is that adaptation mechanisms act only on the dominant motion direction and that they are selectively reduced during a lowered attentional state. Overall, the results demonstrated that conscious perception of an ambiguous motion quartet is highly susceptible to influence from space- and feature-based attentional mechanisms. Still, it was evident that attention does not determine our subjective experience completely; there are other – bottom-up – factors shaping the dynamics of our perceptual interpretation independent of top-down influence.

In Chapter 6, we used a binocular-rivalry paradigm to study attentional influence in a way similar to the experiments in Chapter 5. In binocular rivalry, the two eyes receive competing information and only one interpretation can be consciously perceived. According to one influential account, competition during rivalry is resolved at a relatively early level in the visual hierarchy where interactions between

monocular cells are still possible. Given this assumption, it is reasonable to assume that the involved processes are relatively immune to top-down modulation. In previous studies, it could indeed be shown that the amount of voluntary control is very limited with binocular-rivalry displays. One possible problem with control during rivalry is that voluntary attention might only operate on visible stimuli, which would already limit the time available for modulatory influence, since the input from one eye is strongly inhibited and not available for conscious access during a suppression phase. To study the relevance of visibility for attentional control of rivaling displays, we designed a new grating stimulus, where parts of the stimuli presented to the two eyes were overlapping and others were not (Edge stimulus). In this way, grating parts from both eyes were visible during most of the time in an experimental trial. Observers were instructed to boost the perception of one percept by attending to the outer visible segment of the respective stimulus. The amount of control during this condition was compared to control for a grating stimulus without visible edges (Center stimulus) and to a condition where the interpretations were boosted through changes of fixation position. The results showed no significant difference in control between the Edge and Center conditions. Therefore, visibility does not seem to be the deciding factor for the operation of voluntary attention. A comparison to the fixation condition revealed that this was not due to a ceiling effect. At least for the enhancement of percept durations, the increase due to fixation changes was significantly larger than the increase for the Edge stimulus, suggesting that the display's susceptibility to control through exogenous factors is considerable but cannot be exploited by attention shifts alone. To sum up, a comparison of the results from Chapters 5 and 6 shows that whereas bistable apparent motion is very prone to voluntary control, this is not the case for binocular rivalry. This is surprising because, on a superficial level, the temporal dynamics displayed by those two bistable paradigms is very similar. The differences might arise through the fact that the underlying neural mechanisms (while they are governed by the same dynamics) are implemented on different levels of the visual hierarchy showing different levels of modulation through attentional mechanisms.

As it is often the case in science, the work described in this thesis provides only few answers and leaves more questions than before. An important basic problem for the interpretation of any fMRI result is the relationship between the BOLD signal and the underlying neural activity. Several studies have shown that there is a high correlation between BOLD and single-cell activity, but they could also demonstrate that the correlation is higher between BOLD and local field potentials (LFP), a cumulative signal of synaptic potentials from a large number of cells in the vicinity of the recording electrode. This suggests that BOLD reflects more the input and intra-areal processing of a brain region than the output, a conclusion supported by studies of neurovascular coupling. In addition, other studies found that – at least under non-physiological conditions – the BOLD signal and neural activity can be completely dissociated. What are the implications of those studies for the results reported here? Since it is still unclear whether BOLD and spiking activity can be strongly dissociated under normal physiological conditions in awake animals, it is at least possible that any BOLD effect found in our experiments is largely due to synaptic potentials that are not causing spikes in their neuronal targets. The plausibility of such an alternative depends on the type of activity that has been measured using fMRI. Is there a reason to believe that the signal we measured in our experiments is of a special kind? For the apparent-motion-induced activity in V1 (Chapter 2), this is indeed the case. We argued that the signal we found is most likely caused through feedback projections from hMT/V5+. As a form of top-down modulation, feedback mechanisms have been

associated with changes in oscillatory synaptic potentials controlling the gain of neuronal elements in the target area. Although there is no conclusive evidence yet that feedback activity is fundamentally different from feedforward propagation, it is possible that there is a stronger dissociation between synaptic potentials and spiking activity during feedback processing. This is an exciting hypothesis that can only be addressed through electrophysiological methods that also take into account LFP signals and oscillatory coherence between brain regions or local subregions. Such dissociations between different types of activity would explain why the activation patterns we found in human V1 are inconsistent with measurements of spiking activity in macaque V1 during presentation of apparent-motion stimuli.

Also for the simultaneous fMRI/TMS measurements reported in Chapter 4, the activity modulations in different areas do not necessarily have the same substrate on a neuronal level. In previous fMRI/TMS studies, it could already be demonstrated that TMS effects are not strictly local but also cause BOLD-signal changes in remote and presumably connected areas. This is also clear from peripherally induced movements through motor-cortex TMS; there it is necessary that the activity manages to transcend at least one synapse to cause motor action. On the other hand, the spatial specificity of TMS is high: It can resolve the topographic organization of primary motor cortex as well as the retinotopic layout of early visual cortex. Therefore, TMS does not necessarily induce functionally relevant or suprathreshold effects in remote targets. In addition, the BOLD signal in these remote targets could also be driven by inhibitory processes. Another remarkable aspect of our results in Chapter 4 is the fact that only right-parietal TMS led to considerable BOLD reductions and correlated behavioral deficits. Left-parietal stimulation had almost no measurable consequences. This has implications for both the way TMS and the way our brain works. It suggests that the efficacy of magnetic stimulation is highly dependent on the network properties of the cortical target. Left parietal cortex did show activation in the respective tasks but obviously the application of TMS pulses did not lead to a sufficient destabilization of neuronal processing to result in BOLD and behavioral effects. The most plausible explanation for this is that fast compensatory processes counterbalance the disturbance caused by TMS on a very short timescale. It has been known for a long time that many functions are lateralized to either of the two hemispheres. Especially, a strong asymmetry between left and right parietal cortex has been described in the neglect as well as TMS literature. Our results show how this asymmetry materializes functionally when there is a selective disruption unilaterally in the healthy human brain. Further research is needed to elucidate the mechanisms of and conditions for compensatory processes and also the actual neuronal effects of magnetic stimulation in directly and indirectly affected areas.

Finally, the fundamental objective guiding the experiments in this thesis was the search for the neural correlates of conscious motion perception. An important result from our data on apparent-motion perception in Chapter 2 is that activity in V1 seems to be associated with the conscious perception of the path of illusory movement. This confirms previous results from fMRI studies that used different paradigms to study correlates of consciousness in humans. An important task for the future will be to resolve the contradictory results from electrode recordings in macaques and the above described results for V1. Single-cell activity in macaque V1 is not well correlated with reports of conscious perception, as has been shown in studies on binocular rivalry. There are several explanations for this difference including fundamental discrepancies in brain mechanisms between humans and macaques or factors like the extensive training of macaques and their exceedingly stable eye

movements. For various reasons these arguments do not explain convincingly the divergent results. The most exciting explanation is that the measured signals (BOLD vs. electrode recordings) capture different aspects of processing in the brain. A first major difference between the measurements is one of scale. If one considers that there are about 100000 neurons in one cubic millimeter of cortex (way below the spatial resolution of standard fMRI) and that only 100-200 neurons can be recorded in a single-cell study, it becomes clear that the processing in an area can only be very selectively characterized with electrode recordings. Conversely, BOLD does not provide a direct measurement of neurons' spiking activity. As mentioned above, at least under non-physiological conditions hemodynamic and neuronal signals can be clearly dissociated. Therefore, it is possible that during specific types of brain activity, e.g., top-down modulation in early areas, dissociations between synaptic potentials that drive hemodynamic signals and neural firing can be observed. It will be a major challenge for future studies to demonstrate such dissociations under physiological conditions. This explanation is particularly exciting if one considers recent fMRI studies showing that activity modulations associated with percept changes during binocular rivalry even reach down to the lateral geniculate nucleus of the thalamus pushing down the neural correlates of visual awareness to the earliest stages of processing.

When talking about the neural correlates of consciousness, it is important to agree on which phenomena the term 'consciousness' refers to. A recent discussion in the field of consciousness studies revolves around the issue of whether attention is a necessary concomitant of conscious processing or whether the two can be differentiated. Our psychophysical studies in Chapter 5 and 6 showed that attention can have a major impact on the subjective experience of a bistable apparent-motion stimulus. At the same time, there were other factors determining the dynamics of perceptual changes, suggesting that conscious perception and attention can be at least partly separated. Several recent imaging studies support the idea that different cortical areas as well as different temporal dynamics are associated with awareness and attention. Future studies – on the conceptual as well as the empirical level – will have to disentangle the different aspects of our vague concept of consciousness and find ways to empirically grasp these aspects and their neural correlates.

Samenvatting

De focus van het werk beschreven in dit proefschrift was tweeledig: het eerste, inhoudelijke doel was het uitvinden welke neurale mechanismen betrokken zijn bij de vorming van bewuste bewegingswaarneming, en de manier waarop deze mechanismen gemoduleerd worden door aandacht. Ten tweede verkent het in methodologisch opzicht de mogelijkheden om correlationele en interferende methoden te combineren bij de visualisatie van functionele hersenactivatie, ter beschrijving van de ruimtelijke en temporele kenmerken van visuele cognitieve processen in de mens. De trias van toegepaste methoden bestond uit psychofysisch onderzoek, de visualisatie van taakgerelateerde hersenactiviteit met behulp van magnetische resonantie (functional magnetic resonance imaging, fMRI), en transcraniële magnetische stimulatie (TMS). We hebben aangetoond hoe de unieke informatieve waarde van elk van deze technieken bijdraagt aan vergroting van ons inzicht in de hersenfuncties. Psychofysisch onderzoek biedt een basaal overzicht van het fenomeen en zijn dynamiek, fMRI legt de correlationele structuur bloot tussen stimuli en taken enerzijds, en neurale activiteit anderzijds, en TMS tenslotte biedt de mogelijkheid om selectief te interfereren met verwerkingsprocessen op specifieke lokaties in de hersenschors. Deze drie benaderingen kunnen niet alleen afzonderlijke experimenten toegepast worden, ze zijn ook gecombineerd in één enkele studie zeer waardevol. Elk van de in de voorgaande hoofdstukken beschreven experimenten heeft zijn eigen bijdrage geleverd aan het beantwoorden van de hierboven gedefinieerde onderzoeksvragen. Tegelijkertijd lag bij elk experiment de nadruk ofwel meer op het inhoudelijke, ofwel meer op het methodologische aspect, maar samen genomen geven onze resultaten een coherent beeld van de manier waarop verschillende neurowetenschappelijke methoden gecombineerd kunnen worden om de neurale correlaten van de menselijke visuele cognitie te bestuderen.

In Hoofdstuk 2 beschreven we een fMRI studie die de neurale basis onderzocht van een lange-afstands illusoire beweging in de primaire visuele cortex (V1). In eerder werk werd reeds aangetoond dat het menselijke MT/V5 complex (hMT/V5+), dat cruciaal is voor het verwerken van visuele beweging, een verhoogde respons vertoont wanneer objecten door illusoire beweging verbonden zijn, vergeleken met de respons bij statisch flikkerende objecten op dezelfde lokaties. Dit is zelfs het geval wanneer de beweging en het flikkeren niet gedefinieerd zijn door verschillende stimulusparameters, maar slechts door spontane veranderingen in de bewuste waarneming tijdens fysiek identieke stimulatie. Wij hebben deze benindingen uitgebreid door aan te tonen, naast hMT/V5+, ook V1 betrokken is bij de representatie van illusoire beweging, en meer specifiek in de representatie van het fysiek niet-bestaande bewegingstraject. Aangezien V1 retinotoop georganiseerd is en zijn neuronale elementen een hoge spatiële resolutie hebben, waren wij in staat om de stimulusrepresentaties en de representatie van het illusoire bewegingstraject van elkaar te scheiden. In condities waarin illusoire beweging werd waargenomen was er een significante activatie in de hersengebieden die het bewegingstraject vertegenwoordigden, hoewel deze gebieden niet rechtstreeks geactiveerd werden door de stimuli die de illusie veroorzaakten. Aangezien onze illusoire-bewegingsstimulus een groot gebied van de visuele ruimte omspande, trokken wij de conclusie dat hMT/V5+ de inducerende objecten integreert, en het bewegingsaspect van de stimulus representeert. De activiteit in V1 wordt vervolgens voorgebracht door feedbackmechanismen aangestuurd door hMT/V5+. Slechts door deze recurrente interactie tussen verschillende gebieden ontstaat ons uiteindelijke bewuste percept,

waarbij verschillende aspecten van de stimulus door verschillende corticale arealen gerepresenteerd worden.

Het experiment beschreven in Hoofdstuk 3 onderzocht de dynamiek van bewegingsverwerking in hMT/V5+ met behulp van single-pulse TMS. Met single-pulse TMS kunnen de relevante tijdvensters voor bepaalde corticale processen met millisecondenprecisie onderzocht worden. Dat betekent dat, naast de causale relevantie van een bepaald gebied, ook temporele aspecten van de verwerkingsprocessen achterhaald kunnen worden. Voor hMT/V5+ en bewegingswaarneming leverde de bestaande literatuur conflicterende resultaten wat betreft het tijdstip waarop TMS maximaal zou interfereren. Eén onderzoeksgroep vond een zeer vroeg tijdsvenster van maximale interferentie, rond stimulusaanvang, hetgeen zij interpreteerden als teken van een snelle verwerkingsroute door hMT/V5+, gemediëerd door subcorticale centra. Een alternatief resultatenpatroon werd beschreven in een andere verzameling studies. Daar werd een veel later tijdvenster beschreven, 100-150 ms na stimulusaanvang. Deze bevinding zou meer overeenstemmen met EEG- en MEG-resultaten met betrekking tot bewegingsverwerking in hMT/V5+. Een tekortkoming van de bovengenoemde studies was echter dat de exacte lokalisatie van hMT/V5+ nooit met een onafhankelijke methode was bevestigd. De lokalisatie was doorgaans bepaald aan de hand van vuistregels, uitgaande van standaard EEG-elektrodenposities. Aangezien hMT/V5+ een klein gebied is met een lokalisatie die sterk varieert tussen individuen, is een exacte methode om hMT/V5+ te bepalen van het opperste belang. Daarom was onze benadering om, voorafgaand aan het experiment, hMT/V5+ in de individuele proefpersonen te identificeren met behulp van fMRI. Vervolgens maakten we gebruik van een eerder door ons ontwikkeld stereotactisch positioneringssysteem om TMS toe te passen op de individueel gedefinieerde hMT/V5+. We testten - in stappen van 10 ms - bijna alle mogelijke tijdsvensters van -50 ms voor tot 200 ms na stimulusaanvang. Op deze tijdstippen werd een enkele TMS-puls toegediend, terwijl proefpersonen een taak deden waarbij ze de bewegingsrichting van willekeurig bewegende stippen moesten onderscheiden. Onze resultaten lieten zien dat er een significante prestatieverslechtering optrad rond 130-150 ms na stimulusaanvang, waarmee ze de eerder beschreven resultaten van de tweede groep bevestigden. Er was echter in geen enkel individu een effect voor het 0 ms tijdsvenster, zoals beschreven door de eerste groep. Deze studie laat zien hoe MRI technieken gebruikt kunnen worden om TMS toe te passen op specifieke doellokaties in individuele proefpersonen. Alleen door onafhankelijke bevestiging van de TMS-spoellokatie ten opzichte van functioneel gedefinieerde hersengebieden kan een objectieve methodologie voor het plaatsen van de TMS-spoel worden bereikt.

De experimenten beschreven in de twee voorgaande hoofdstukken demonstreerden de unieke bijdragen die fMRI en TMS kunnen leveren, zowel onafhankelijk als in seriële combinatie. In het vierde hoofdstuk hebben we de mogelijkheden onderzocht die het simultaan combineren van fMRI en TMS kan bieden. De techniek van het toedienen van magnetische stimulatie in de MRI-scanner werd pas recentelijk ontwikkeld. De eerste studies op dit gebied richtten zich op het verbeteren van de experimentele opzet en gebruikten simpele paradigma's, vooral met betrekking op het motorisch systeem, om de technieken te valideren. In onze studie wilden we de toepassing van de fMRI/TMS combinatie uitbreiden naar meer cognitieve taken. De functionele beperking die TMS in zulke taken teweegbrengt tijdens deze taken wordt ook wel een 'virtuele laesie' genoemd, maar tot nu toe konden de neuronale consequenties van deze verstoring niet aangetoond worden. Ons doel was daarom om de versterkende of juist onderdrukkende effecten

van TMS op het bloed-zuurstofgehalte-afhankelijke (blood-oxygenation-level-dependent) signaal, oftewel BOLD-signaal, te visualiseren met behulp van een gelijktijdige fMR meting, en deze veranderingen te vergelijken met het gemeten gedrag van de proefpersonen. We gebruikten een visuospatiële taak die was onderzocht in eerdere fMRI en TMS studies, en die grotendeels afhankelijk is van verwerking in de superieure pariëtale cortex. Gedurende deze taak moesten proefpersonen de hoek tussen de wijzers van een kortstondig getoonde analoge klok inschatten. Als controleconditie voor niet-taakspecifieke TMS-effecten lieten we de proefpersonen een kleurendiscriminatietaak uitvoeren op hetzelfde stimulusmateriaal. In afzonderlijke sessies werd TMS toegepast op de rechter en linker pariëtale cortex (respectievelijke elektrodeposities 'P4' en 'P3') gedurende het scannen. Bij rechts-pariëtale stimulatie vonden we een onderdrukking van de BOLD-respons op de gestimuleerde plaats, maar ook in verder verwijderde gebieden die waarschijnlijk verbonden zijn met de pariëtale cortex, met name de middelste frontale gyrus. Opvallend was dat deze onderdrukking tevens waarneembaar was tijdens de kleurendiscriminatietaak, hoewel veel minder sterk. Enkel voor de superieure pariëtale cortex en de middelste frontale gyrus werd een zeer hoge correlatie tussen het BOLD-effect en de gedragsmatige veranderingen gevonden. De gedragsmatige verandering, bestaande uit toegenomen reactietijden, was eveneens alleen significant in de hoekschattingstaak. In contrast hiermee stond het uitblijven van enige consequentie bij links-pariëtale stimulatie, hetgeen een specialisatie van de rechter pariëtale cortex voor visuospatiële verwerking suggereert. Naast de hemisferische specialisatie maken onze data aannemelijk dat de effecten van TMS niet beperkt blijven tot de gestimuleerde lokatie, maar dat ze waargenomen kunnen worden in een netwerk van verbonden corticale gebieden die waarschijnlijk relevant zijn voor de uitgevoerde taak. Daarnaast is duidelijk geworden dat het toepassen van TMS op een bepaalde plaats niet noodzakelijkerwijze leidt tot een modulatie van het BOLD-signaal: links-pariëtale stimulatie leidde niet tot enige waarneembare reductie in het BOLD-signaal. Dit zou impliceren dat een BOLD-effect alleen zichtbaar is wanneer het gestimuleerde gebied ook daadwerkelijk essentieel is voor het uitvoeren van de taak, óf dat de verstoring van activiteit in het netwerk tenminste gedeeltelijk teniet gedaan kan worden door compensatoire mechanismen in andere hersengebieden.

De studies in de laatste twee hoofdstukken van dit proefschrift hadden betrekking op een recent debat over de relatie tussen aandacht en bewustzijn, dat zowel in filosofische als neurowetenschappelijke kringen gaande is. Traditioneel werden deze fenomenen als onlosmakelijk verbonden beschouwd: Men kon zich niet bewust zijn van iets waarop de aandacht niet gericht was. Verschillende auteurs hebben echter beargumenteerd dat er wel degelijk onderscheid tussen de twee gemaakt moet worden, zowel op conceptuele als op empirische gronden. Data van verschillende experimenten laten zien dat het mogelijk is de effecten van aandacht en bewustzijn te scheiden, en pleiten daarmee voor een relatieve onafhankelijkheid van de onderliggende mechanismen. De laatste twee hoofdstukken van dit proefschrift richtten zich op het psychofysisch onderzoeken van de interactie tussen aandacht en bewustzijn, met name de hoeveelheid controle die we kunnen uitoefenen over onze bewuste waarneming van ambiguë stimuli. De twee series van experimenten maakten gebruik van verschillende paradigma's – illusoire beweging en binoculaire rivaliteit – die beide reeds eerder intensief gebruikt werden in experimenten die de neurale correlaten van visueel bewustzijn onderzochten.

In Hoofdstuk 5 gebruikten we het zogenaamde 'bewegingskwartet', een illusoire-bewegingsstimulus die de perceptie van ofwel horizontale, ofwel verticale beweging

veroorzaakt. De op een bepaald moment waargenomen bewegingsrichting kan spontaan veranderen, waarschijnlijk als gevolg van adaptatiemechanismen. In twee experimenten onderzochten we hoe waarnemers hun perceptie kunnen manipuleren aan de hand van ontvangen instructies, en hoe manipulatie van spatiële aandacht het optreden van spontane veranderingen beïnvloedt. In Experiment 1 werden proefpersonen geïnstrueerd om de richtingsveranderingen te versnellen, om passief naar de stimulus te kijken, of om de veranderingen te vertragen. De proefpersonen toonden een opvallend vermogen tot het uitoefenen van controle: Ze waren in staat om de duur van een bepaald percept haast te verdubbelen of te halveren ten opzichte van de passieve waarneming. Verdere analyse liet zien dat de temporele kenmerken van de veranderingen vergelijkbaar waren gedurende alle condities, wat suggereert dat de controle over het percept niet volledig door de wil van de proefpersoon werd beheerst. In het tweede experiment werd de spatiële aandacht afgeleid van de stimuli door in het fixatiepunt een aandachtsintensieve detectietaak aan te bieden. Terwijl ze de taak uitvoerden moesten de proefpersonen nog steeds hun bewuste waarneming rapporteren. Wanneer de aandacht was afgeleid van het bewegingskwartet duurden de percepten gemiddeld ongeveer 80% langer. Dit betekent dat wanneer spatiële aandacht wordt weggeleid van de stimuli, het huidige percept stabiel blijft. Een mogelijke interpretatie is dat adaptatiemechanismen alleen inwerken op de dominante bewegingsrichting, en dat ze selectief gereduceerd zijn gedurende een periode van verminderde aandacht. Over het geheel genomen toonden de resultaten aan dat bewuste waarneming van een ambigu bewegingskwartet zeer ontvankelijk is voor ruimtelijke en kenmerk-gerelateerde aandachtsmechanismen. Desondanks was ook duidelijk dat aandacht niet volledig bepalend is voor onze subjectieve ervaring; er zijn andere – bottom-up - factoren die, onafhankelijk van top-down invloeden, vormgeven aan onze perceptuele interpretatie.

In Hoofdstuk 6 gebruikten we een binoculair-rivaliteitsparadigma om de invloed van aandacht te bestuderen, op een vergelijkbare manier als in Hoofdstuk 5. Bij binoculaire rivaliteit ontvangen beide ogen tegenstrijdige informatie, terwijl er slechts één interpretatie bewust kan worden waargenomen. Een invloedrijke visie hierop is dat de competitie reeds op een relatief vroeg niveau in de visuele hiërarchie beslecht wordt, wanneer interacties tussen de monoculaire cellen nog mogelijk zijn. Uitgaande van dit standpunt kan aangenomen worden dat de processen die hierbij betrokken zijn relatief immuun zijn voor top-down modulatie. In voorgaande studies werd inderdaad aangetoond dat er slechts in zeer beperkte mate controle uitgeoefend kan worden over een situatie van binoculaire rivaliteit. Een potentieel probleem met betrekking tot wilsgestuurde controle gedurende binoculaire rivaliteit is dat de aandacht mogelijk alleen gericht kan worden op zichtbare stimuli, wat de voor modulatie beschikbare tijd reeds sterk zou begrenzen, aangezien de input van één oog sterk geïnhibeerd wordt en tijdens deze onderdrukkingsfase niet beschikbaar is voor bewuste verwerking. Om het belang van zichtbaarheid voor de controle over rivaliserende visuele input te kunnen bestuderen ontwierpen we een nieuwe rasterstimulus, waarbij gedeelten van de stimuli die aan de twee ogen gepresenteerd werden overlapten, en gedeelten niet (Rand stimulus). Op deze manier waren gedeelten van het raster voor beide ogen zichtbaar gedurende het grootste gedeelte van het experiment. Proefpersonen werden geïnstrueerd om de waarneming van een van de percepten te verhogen door hun aandacht te richten op het buitenste zichtbare segment van de respectievelijke stimulus. De hoeveelheid controle gedurende deze conditie werd vergeleken met een controlestimulus, een raster zonder zichtbare randen (Centrum stimulus), en met een conditie waarin de

interpretaties werden gestimuleerd door middel van variaties in de positie van het fixatiepunt. De resultaten lieten geen significant verschil zien met betrekking tot de hoeveelheid uitgeoefende controle tussen de Rand en Centrum condities. Zichtbaarheid is dus blijkbaar niet de bepalende factor in het sturen en controleren van vrijwillige aandacht. Een vergelijking met de fixatieconditie liet zien dat dit niet te wijten was aan een plafondeffect. Voor zover het de vergroting van de duur van de percepten betrof, was de toename als gevolg van variaties in de fixatiepositie significant groter dan de toename bij de Rand stimulus. Dit suggereert dat de ontvankelijkheid van het display voor controle door exogene factoren aanzienlijk is, maar niet alleen door verplaatsing van de aandacht benut kan worden. Samenvattend kan gezegd worden dat een vergelijking van de resultaten uit Hoofdstuk 5 en 6 laat zien dat terwijl bistabiele illusoire beweging zeer vatbaar is voor wilsgestuurde controle, dit niet het geval is voor binoculaire rivaliteit. Dit is verrassend, omdat de temporele kenmerken van de beide bistabiele paradigma's oppervlakkig beschouwd sterke overeenkomsten vertonen. De verschillen ontstaan wellicht doordat de onderliggende neurale mechanismen (hoewel beheerst door dezelfde dynamica) geïmplementeerd zijn op verschillende niveaus van de visuele hiërarchie, die verschillende niveaus van aandachtsgerelateerde modulatie vertonen.

Zoals zo vaak het geval is wanneer het de wetenschap betreft verschaft het in dit proefschrift beschreven werk slechts enkele antwoorden, en zorgt het voor des te meer nieuwe vragen. Een belangrijk fundamenteel probleem voor het interpreteren van welk fMRI-resultaat dan ook is de relatie tussen het BOLD-signaal en de neurale activiteit die daaraan ten grondslag ligt. Verschillende studies hebben reeds aangetoond dat er een hoge correlatie is tussen BOLD en de activiteit van afzonderlijke neurale cellen. Ze hebben echter ook aangetoond dat er een hogere correlatie bestaat tussen BOLD en het locale veldpotentiaal (local field potential, LFP), een cumulatief signaal opgebouwd uit de synaptische potentialen van een groot aantal cellen in de buurt van de opname-elektrode. Dit doet vermoeden dat BOLD eerder een reflectie is van de input en intra-areale verwerking, dan van de output van een bepaald hersengebied, een conclusie die ondersteund wordt door studies naar neurovasculaire koppeling. Bovendien hebben andere studies gevonden dat – tenminste onder niet-fysiologische omstandigheden – het BOLD-signaal en neurale activiteit compleet van elkaar gedissocieerd kunnen worden. Wat zijn nu de implicaties van deze studies voor de hier gerapporteerde resultaten? Aangezien het nog steeds onduidelijk is of het BOLD-signaal en het vuren van neuronen inderdaad sterk van elkaar kunnen afwijken onder normale fysiologische condities in wakkere dieren, is het op zijn minst mogelijk dat elk van de in onze studies gevonden BOLD-effecten grotendeels toegeschreven kan worden aan synaptische potentialen die geen output, en dus geen vuuractiviteit veroorzaken in hun neuronale doelwit. De plausibiliteit van een dergelijke alternatieve verklaring is afhankelijk van het type activiteit dat gemeten werd met behulp van fMRI. Is er enige reden om aan te nemen dat het signaal dat in onze experimenten gemeten werd er een is van een speciaal type? Met betrekking tot de activiteit in V1 die veroorzaakt werd door illusoire beweging (Hoofdstuk 2) is dit inderdaad het geval. We voerden aan dat het door ons gevonden signaal zeer waarschijnlijk veroorzaakt wordt door feedback geprojecteerd vanuit hMT/V5+. Feedbackmechanismen, als een vorm van top-down modulatie, zijn geassocieerd met veranderingen in oscillerende synaptische potentialen, die de versterkingsfactor van neuronale elementen in het doelgebied controleren. Hoewel er nog geen sluitend bewijs is dat feedback fundamenteel verschilt van feedforward activiteit, is het mogelijk dat er gedurende feedback een sterkere dissociatie is tussen synaptische potentialen en neuronaal vuren. Deze interessante hypothese kan

slechts beproefd worden met behulp van elektrofysiologische onderzoeksmethoden, die ook rekening houden met LFP-signalen en oscillatoire coherentie tussen hersengebieden of locale subgebieden. Zulke dissociaties tussen verschillende typen van activiteit zouden kunnen verklaren waarom de activatiepatronen die we vonden in de menselijke V1 inconsistent zijn met metingen van neuronaal vuren in V1 van makaken gedurende de presentatie van illusoire-bewegingsstimuli.

Ook met betrekking tot de simultane fMRI/TMS-metingen die in Hoofdstuk 4 gepresenteerd werden, hoeven de modulaties van de activiteit in verschillende gebieden niet hetzelfde neurale substraat te hebben. In eerdere fMRI/TMS-studies werd reeds aangetoond dat de effecten van TMS niet strikt lokaal zijn, maar dat de toepassing ook BOLD-signalen verandert in elders gelegen corticale gebieden, die waarschijnlijk verbonden zijn met het gestimuleerde gebied. Dit wordt tevens duidelijk door perifeer veroorzaakte bewegingen als gevolg van TMS toegepast op de motorische cortex; in dat geval moet de activiteit tenminste één synaps passeren om een motorische actie te bewerkstelligen. Aan de andere kant heeft TMS een zeer hoge spatiële specificiteit: het kan de topografische organisatie van de primaire motorische cortex blootleggen, evenals de retinotopische indeling van de vroege visuele cortex. TMS hoeft dus niet noodzakelijkerwijs functioneel relevante of drempeloverstijgende effecten te bewerkstelligen in elders gelegen doelgebieden. Daarnaast kunnen de BOLD-signalen in deze elders gelegen doelgebieden ook nog inhibitoire processen weerspiegelen. Een ander opvallend aspect van de resultaten beschreven in Hoofdstuk 4 is het feit dat alleen rechts-pariëtale TMS resulteerde in noemenswaardige BOLD-reducties en de gedragsmatige verstoringen die daarmee samenhangen. Links-pariëtale stimulatie had nauwelijks meetbare gevolgen. Dit gegeven heeft implicaties voor de manier waarop zowel ons brein, als TMS werken. Het suggereert dat de uitwerking van magnetische stimulatie sterk afhankelijk is van de netwerk-eigenschappen van het corticale doelgebied. Links-pariëtale cortex vertoonde wel activatie tijdens de betreffende taak, maar het toedienen van TMS-pulsen veroorzaakte onvoldoende destabilisatie in de neurale verwerking om verandering aan te brengen in de BOLD- en gedragsmatige effecten. De meest plausibele verklaring hiervoor is dat snelle, compensatoire processen het verstorende effect van TMS op zeer korte termijn neutraliseren. Het is reeds lang bekend dat vele functies gelateraliseerd zijn naar een van beide hemisferen. Tussen linker en rechter pariëtaalcortex in het bijzonder is er een sterke asymmetrie beschreven in zowel neglect- als TMS-literatuur. Onze resultaten laten zien hoe een dergelijke asymmetrie functioneel tot uiting komt wanneer er unilateraal in het gezonde menselijke brein een selectieve verstoring is. Verder onderzoek is nodig om licht te werpen op de mechanismen en voorwaarden voor het optreden van compensatoire processen. Hetzelfde geldt voor de werkelijke neuronale effecten van magnetische stimulatie in direct en indirect getroffen gebieden.

De fundamentele doelstelling die de leidraad vormde voor de in dit proefschrift beschreven experimenten was de zoektocht naar de neurale correlaten van de bewuste perceptie van beweging. Een belangrijk resultaat uit onze onderzoeksgegevens met betrekking tot het waarnemen van illusoire beweging, zoals beschreven in Hoofdstuk 2, is dat activiteit in V1 samen blijkt te hangen met de bewuste perceptie van het afgelegde traject van de bewegingsillusie. Dit komt overeen met resultaten van eerder uitgevoerde fMRI-studies, die aan de hand van verschillende paradigma's de correlaten van het menselijke bewustzijn bestudeerden. Een belangrijke opgave voor de toekomst is het het oplossen van de tegenstrijdige resultaten van elektroderegistraties in makaken en de eerder beschreven resultaten in V1. De activiteit van afzonderlijke cellen in V1 van makaken

correleert niet hoog met resultaten met betrekking tot bewuste perceptie, zoals aangetoond werd met behulp van de studies naar binoculaire rivaliteit. Er zijn verschillende mogelijke verklaringen voor dit onderscheid, waaronder een fundamentele discrepantie tussen mensen en makaken, en factoren zoals de intensieve training van makaken, en hun uitzonderlijk stabiele oogbewegingen. Om verschillende redenen vormen deze argumenten echter geen overtuigende verklaring voor de uiteenlopende resultaten. De meest opwindende verklaring is dat de gemeten signalen (BOLD- versus elektrodesignalen) verschillende aspecten van de verwerking in het brein weerspiegelen. Een eerste belangrijk verschil tussen de beide metingen is hun schaal. In aanmerking genomen dat een kubieke millimeter cortex (hetgeen al beduidend minder is dan de spatiële resolutie van standaard fMRI) ongeveer 100.000 neuronen bevat, en dat een 'single cell'-opname slechts de activiteit van 100 tot 200 neuronen registreert, is het duidelijk dat de verwerking in een bepaald gebied slechts zeer selectief gerepresenteerd kan worden door middel van elektrodeopnamen. BOLD, daarentegen, biedt geen directe weergave van het vuurgedrag van neuronen. Zoals eerder vermeld kunnen, tenminste onder niet-fysiologische omstandigheden, hemodynamische en neuronale signalen duidelijk van elkaar onderscheiden worden. Het is dus mogelijk dat er tijdens bepaalde typen van hersenactiviteit, zoals top-down modulatie in vroege gebieden, dissociaties waarneembaar zijn tussen de synaptische potentialen die het hemodynamisch signaal aansturen en het neuraal vuren. Voor toekomstige studies zal het een grote uitdaging zijn om zulke dissociaties onder fysiologische condities aan te tonen. Deze verklaring is des te interessanter in het licht van recente fMRI-studies, die aantoonden dat de modulatie van activiteit als gevolg van veranderingen in het percept gedurende binoculaire rivaliteit zelfs doordringt tot de laterale geniculate nucleus van de thalamus, waarmee de neurale correlaten van visueel bewustzijn terug worden geleid tot de vroegste stadia van verwerking.

Wanneer we het hebben over de neurale correlaten van bewustzijn is het van groot belang om duidelijk te stellen aan welke fenomenen de term 'bewustzijn' precies refereert. Een recente discussie in kringen van bewustzijnsonderzoek draait om de vraag of aandacht een noodzakelijk begeleidend fenomeen is voor bewuste verwerking, of dat de twee gedifferentieerd kunnen worden. Onze psychofysische studies beschreven in Hoofdstuk 5 en 6 lieten zien dat aandacht een aanmerkelijke invloed kan hebben op de subjectieve ervaring van bistabiele illusoire-bewegingsstimuli. Tegelijkertijd waren er andere factoren die de dynamiek van de perceptuele veranderingen bepaalden, hetgeen suggereert dat bewuste waarneming en aandacht op zijn minst gedeeltelijk gescheiden kunnen worden. Verschillende recente studies die hersenactivatie visualiseerden, ondersteunen het idee dat bewustzijn en aandacht zowel verschillende corticale gebieden rekruteren, als een verschillende temporele dynamiek vertonen. Toekomstige studies, op conceptueel én empirisch vlak, zullen moeten proberen om de diverse aspecten van het vage concept van bewustzijn te ontwarren, en manieren te vinden om deze aspecten en hun neurale correlaten empirisch te kunnen vatten.

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Curriculum Vitae

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